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REVIEW ARTICLE

Drug-drug interactions of the reserve antibiotics: a narrative review

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Summary

Drug interactions often cause side effects, especially in children, elderly and/or patients with chronic diseases. Antibiotics are among the most commonly used drugs, so potential impact of antibiotic-drug interactions on the ultimate outcome of therapy may be of great clinical value. Bearing in mind that antibiotic-drug interactions can lead to development of antimicrobial resistance (AMR), their identification is specifically important for reserve antibiotics. The aim of this narrative review is to analyze the drug-drug interaction potential of reserve antibiotics. The highest potential for antibiotic-drug interactions was identified with linezolid, colistin, dalfopristin/quinupristin, lefamulin and oritavancin. Special caution should be paid to concomitant administration of ceftazidime-avibactam, telavancin, colistin, polymyxin B, plazomicin with drugs that have nephrotoxic potential due to possibility of more severe renal impairment. Exceptional wariness is required when combining drugs with reserve antibiotics with limited drug-drug interactions information such as plazomicin, carumonam, iclaprim. Having in mind that antibiotic-drug interaction can lead to the changed antimicrobial efficiency and/or safety of the therapy, the antibiotic choice has to be based on data regarding interaction potential. Continuous education of clinical staff regarding the choice of antibiotics based on their interaction potential and optimizing the antibiotic dose may significantly improve pharmacotherapy and decrease the risk for AMR.

Keywords: antibiotic, drug-drug interactions, reserve antibiotics, AMR

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INTRODUCTION

Drug-drug interactions (DDIs) are caused by the co-administration of multiple drugs and may lead to altered drug concentration, raising numerous questions regarding safety and effectiveness (1). DDIs are more often observed in vulnerable populations such as children, elderly and/or patients with chronic diseases due to polypharmacy, multi-comorbidities, frequent use of off-label drugs and special dosage regime (2-5).

Antibiotics are among the most commonly used drugs, so potential impact of antibiotic-drug interactions are of great clinical value (6, 7). Antibiotic interactions may be divided into those that affect the pharmacokinetic profile of the drug and those that affect the pharmacodynamic profile of the drug (8). Pharmacodynamic interactions can be classified into synergistic or antagonistic interactions, depending on whether the drug combination leads to increased or decreased antibiotic activity (8). So far, the most widely studied mechanism for pharmacokinetic antibiotic-drug interactions is the inhibition or induction of drug metabolizing enzymes. Besides the well- known role of cytochrome P450 (CYP450) in antibiotic-drug interaction, recently special caution has been given to the role of transmembrane proteins: P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter (OAT) (8). Depending on which substrate antibiotics interact with, we can divide interactions into several groups: antibiotic-drug, antibiotic-redox active metal, antibiotic-food, or antibiotic-disease interactions (2, 6, 7). Bearing in mind increased antibiotic consumption in our country (9), more frequent antibiotic-drug interactions are expected. Furthermore, since antibiotic-drug interactions can lead to suboptimal antibiotic plasma concentration and to the development of antimicrobial resistance (AMR), their identification is of great value, especially for the group of reserve antibiotics (6, 7). In order to optimize antibiotic stewardship efforts at the local, national and international levels, the World Health Organization (WHO) Expert Committee developed the AWaRe Classification of antibiotics in 2017, which was later updated in 2021. According to the AWaRe Classification antibiotics are classified into three groups: Access, Watch and Reserve, based on their impact on antimicrobial resistance. The Access group includes antibiotics recommended as the first or second choice for infections caused by the most encountered susceptible pathogens, with lower resistance potential compared to the other two groups. The Watch group includes antibiotics that have higher resistance potential and are recommended for use only in a limited number of specific infectious syndromes. The Reserve group, so called "last resort", includes antibiotics that should be saved for the infections caused by multidrug-resistant microorganisms (10).

Recently published study showed a high proportion of multidrug-resistant strains of *Klebsiella pneumoniae* (*K. pneumoniae*) and *Escherichia coli* (*E. coli*) in the Republic of Serbia (RS) (9). These strains are mostly responsible for deaths attributable to AMR worldwide (9). In addition, research highlights the need for expanding the list of reserve group of antibiotics in RS. In January 2024, only 8 out of total 29 reserve antibiotics were registered in RS. Furthermore, only 5 reserve antibiotics listed on WHO Model List of Essential Medicines (EML) 2023 are registered in RS: ceftazidime/avibactam, ceftolozane/tazobactam, colistin, linezolid, meropenem/vaborbactam.

The aim of this narrative review is to analyze the drug interaction potential of the reserve group of antibiotics. By using information about potential antibiotic interactions in daily practice, we can prevent the ineffectiveness of therapy and side effects, and what is even more important, reduce the possibility of developing AMR for antibiotics that represent the last line defense for difficult-to-treat pathogens.

BETA-LACTAMS

Cephalosporins

Ceftazidime-avibactam is a combination of third-generation cephalosporin and novel, non-β-lactam β-lactamase inhibitor available in RS. It is approved for the treatment of adults with complicated urinary tract infections (cUTIs), complicated intra-abdominal infections (cIAIS), hospital-acquired pneumonia (HAP), and other infections caused by aerobic Gram-negative organisms in patients with limited treatment options (11). Avibactam does not inhibit P450 enzymes, while ceftazidime-avibactam does not inhibit the major renal or hepatic transporter nor has the potential to induce P450 enzymes (12). In *in vitro* settings, avibactam is a substrate for OAT1 and OAT3 transporters, therefore concomitant use of a potent inhibitor of OAT transporter, such as probenecid, may alter the elimination of avibactam (13). Concomitant use of ceftazidime-avibactam and drugs that have nephrotoxic potential may alter renal function (14). *In vitro,* chloramphenicol is an antagonist with ceftazidime-avibactam. Despite the absence of clinical relevance of these findings, the mentioned drug combination is not advised (12, 14). Synergistic interactions were observed when ceftazidime-avibactam was administered with colistin, tobramycin, tigecycline, aztreonam, meropenem, and imipenem (15, 16, 17). **(Table 1)**.

Ceftolozane-tazobactam

Ceftolozane-tazobactam is a combination of a novel semi-synthetic broad-spectrum fifth generation cephalosporin and well-known β-lactamase inhibitor tazobactam, available in RS (18). It is approved for treatment of cIAIs, acute pyelonephritis, cUTIs, HAP, including

Table 1. Potential drug-drug interactions involving novel antibiotics.

Drug A	Drug B	The effect
Ceftazidime-avibactam	Aminoglycosides, furosemide, high doses of cephalosporin Chloramphenicol Probenecid	Adverse effects on renal function Antagonists ↑ avibactam concentration
Ceftolozane-tazobactam	Probenecid	↑ tazobactam concentration
Cefiderocol	CYP3A4 substrates (hormonal contraceptives)	↓ systemic exposure of CYP3A4 substrates
Ceftobiprole-medocaril	Warfarin	↑ INR and PT
Meropenem-vaborbactam	Probenecid CYP2D6 substrates Valproic acid Warfarin	↑vaborbactam concentration ↓concentration of CYP2D6 substrates ↓ concentration of valproic acid ↑ anticoagulant effects
Imipenem/cilastatin-relebactam	Ganciclovir Valproic acid Warfarin	Generalized seizures ↓ concentration of valproic acid ↑ anticoagulant effects
Faropenem	Probenecid	Prolongs the exposure duration of faropenem
Aztreonam	Cefoxitin and Imipenem Ceftazidime-avibactam	Antagonists Synergism
Oritavancin	CYP2C9 and CYP2C19 substrates CYP3A4 and CYP2D6 substrates	↑ concentration of CYP2C9 and CYP2C19 substrates ↓ concentration of CYP3A4 and CYP2D6 substrates
Telavancin	Nephrotoxic agents Clotting tests	↑ Nephrotoxic potential ↑ INR and aPTT
Daptomycin	Ampicillin-sulbactam Piperacillin-tazobactam Ticarcillin/clavulanate Oxacillin Vitamin E Drugs that reduce renal filtratiton (NSAID and COX2 inhibitors)	Synergistic interaction Synergistic interaction Synergistic interaction Synergistic interaction Immunomodulatory effect ↑concentrations of daptomycin
Fosfomycin IV	Linezolid Ciprofloxacin Ceftriaxone Metoclopramide	Synergistic interactions Synergistic interactions Synergistic interactions ↓ Fosfomycin IV
Dalfopristin/quinupristin	Cyclosporin CYP3A4 metabolized drugs	↑dalfopristin/quinupristin concentration ↑ plasma concentration that undergoesCYP3A4 metabolism (antihistamines, anti-HIV, antineoplastic drugs, benzodiazepines, calcium channel blockers, cholesterol-lowering agents, gastrointestinal tract motility agents, immunosuppressive agents and steroids)
Linezolid	Pseudoephedrine and phenylpropanolamine Serotonergic agents Rifampicin Warfarin	↑ blood pressure Serotonin syndrome ↓ linezolid concentration ↓ INR
Tedizolid	BCRP substrates	↑ concentration of BCRP substrates
Lefamulin	Amiodarone, Ia and III antiarrythimcs, antipsychotics, tricyclic antidepressants, fluoroquionolones, macrolides, verapamil, azoles, protease inhibitors Rifampicin, *Hypericum perforatum*, carbamazepine, phenytoin, primidone CYP3A inhibtors, P-gp inhibitors and CYP2C8 metabolized drugs	↑ QT interval ↓ Lefamulin concentration ↑ Lefamulin concentration
Minocycline-IV	Antacids Isotretinoin Ergot alkaloids Anticoagulants Diuretics and oral contraceptives	↓Absoroption of tetracycline Pseudotumor cerebri Acute limb ischemia and ergotism ↓ PT ↑ side effects
Tigecycline	Calcineurin inhibitors Amikacin, ampicillin/sulbactam, piperacillin/tazobactam, minocycline, rifampicin	↑ concentration of calcineurin inhibitors Synergistic interactions
Eravacycline	CYP3A4 inducers	↓ eravacycline concentration
Colistin	Non-depolarising muscle relaxants Neurotoxic agents Nephrotoxic agents Aminoglycosides, fluoroquinolones	Prolonged effects of muscle relaxants ↑ neurotoxic potential ↑ nephrotoxic effects Deterioration of Myasthenia Gravis
Polymyxin-B	Nephrotoxic agents	↑ Nephrotoxic potential
Plazomicin	Nephrotoxic agents	↑ Nephrotoxic potential

↑ - increased; ↓ - decreased; CYP – cytochrome P450; P-gp – P-glycoprotein; INR - international normalized ratio; BCRP - breast cancer resistance protein; PT- prothrombin time; aPTT – activated partial thromboplastin time;

ventilator-associated pneumonia (VAP) (19). Based on *in vitro* and *in vivo* published studies, no interactions were observed with substrates, inhibitors, and inducers of CYP450 enzymes when ceftolozane-tazobactam was administered in therapeutic doses (19). Similar to avibactam, tazobactam is a substrate for OAT1 and OAT3 and concomitant use with a potent OAT inhibitor may increase tazobactam plasma concentrations (19). So far, synergistic, or additive interactions have been observed between ceftolozane-tazobactam and fosfomycin, aztreonam, amikacin, tigecycline, colistin, and meropenem (20-22).

Ceftaroline fosamil

Ceftaroline fosamil is a "fifth-generation" cephalosporin (23). It is indicated in the treatment of complicated skin and soft tissue infections (cSSTIs) and community-acquired pneumonia (CAP) (24). *In vitro* studies showed that ceftaroline is not a substrate, inhibitor, or inducer of major CYP450 enzymes (24). Furthermore, population pharmacokinetic analysis demonstrated no interactions between ceftaroline and drugs that are inhibitors, inducers, or substrates of the cytochrome P450 system (24). As clinical studies regarding ceftaroline fosamil's interaction potential are not completed yet, the drug should be used cautiously.

Cefiderocol

Cefiderocol (S-649266), a novel cephalosporin, stands out due to its unique chemical structure featuring a chlorocatechol ring that enables it to penetrate bacteria through iron channels and is indicated for the treatment of infections caused by Gram-negative organisms in adults with limited treatment options (25). Adding clinically available serine β-lactamase inhibitors to cefiderocol might represent a significant formulation development to broaden its spectrum and therapeutic effectiveness while curbing *in vivo* resistance emergence (26). The combination of cefiderocol with β-lactamase inhibitors, especially avibactam, has a synergistic effect against resistant *Acinetobacter baumannii (A. baumanii)*. Similarly, *in vitro* synergy has been observed when cefiderocol is combined with meropenem, amikacin, tigecycline, and minocycline (27). Notably, cefiderocol has no clinically significant interference with various anion and cation organic transporters such as OAT, organic cation transporters (OCT), multidrug and toxic extrusion (MATE), organic anion transporting polypeptides (OATP) and BCRP. *In vitro*, cefiderocol induces CYP3A4 activity and to a lesser extent, CYP2C and P-gp (27). The metabolism of co-administered medicines that are substrates of CYP3A4 is increased, leading to decreased systemic exposure of these drugs, as is the case with hormonal contraceptives (27). The clinical relevance of cefiderocol's induction of CYP2C and P-gp is unknown.

Ceftobiprole-medocaril

Ceftobiprole-medocaril represents an innovative parenteral cephalosporin belonging to the fifth generation. It is indicated for the treatment of HAP (excluding VAP), and CAP (28). It is the water-soluble prodrug of ceftobiprole (28). Ceftobiprole is neither a substrate nor an inhibitor of P-gp (29). The drug undergoes minimal metabolism, does not induce CYP isoenzymes and its supratherapeutic concentrations minimally inhibits CYP isoenzymes such as CYP1A2, CYP2B6, CYP2C19, CYP3A4/5 (29). Ceftobiprole-medocaril is primarily eliminated through glomerular filtration and it seems that it is not eliminated via active tubular secretion (29). As a result, no anticipated interactions are foreseen in the renal excretion of the medication (29). There is an interaction between ceftobiprole-medocaril and warfarin, which is reflected in an increased prothrombin time and an International Normalized Ratio (INR) (30).

CARBAPENEMS

Two approved carbapenem-β-lactamase inhibitor combinations by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) are meropenem-vaborbactam and imipenem-cilastatin/relebactam (31). Meropenem-vaborbactam is among five reserve antibiotics listed on WHO Model EML registered in RS. It is indicated for the treatment of cUTIs, including pyelonephritis, cIAIs, HAP, including VAP (32). It is also indicated for the therapy of infections due to aerobic Gram-negative organisms in adults with limited therapeutic options (32). *In vitro* data demonstrated the potential of meropenem-vaborbactam to induce CYP1A2, CYP3A4, and potentially other pregnane X receptor (PXR)-regulated enzymes and transporters (32). Concomitant use of meropenem-vaborbactam and medications that are predominantly metabolised by mentioned enzymes may lead to decreased plasma concentration of the co-administered medical products (32). Meropenem-vaborbactam is a substrate of OAT3 and co-administration of OAT3 inhibitors, such as probenecid, may increase antibiotic plasma concentration (33).

Imipenem/cilastatin-relebactam is approved for the treatment of HAP, including VAP, bacteremia suspected or in association with HAP or VAP, infections due to aerobic Gram-negative organisms in adults with limited treatment options (34). No clinically significant interactions between imipenem/cilastatin-relebactam and OAT inhibitors were observed (35). Concomitant administration of carbapenems and valproic acid is associated with reductions in valproic acid concentrations, and increased risk of breakthrough seizures (36). In addition, generalized seizures have been reported in patients receiving imipenem/cilastatin and ganciclovir (35). Simultaneous

administration of antibacterial agents, such as meropenem-vaborbactam or imipenem-cilastatin/relebactam, with warfarin may lead to increased anticoagulant effects, therefore it is recommended to monitor INR during and shortly after co-administration of antibacterials with warfarin (32, 34). Meropenem-vaborbactam may decrease the efficacy of hormonal contraceptives containing estrogen and/or progesterone, and alternative contraceptive methods are generally advised during therapy with broad-spectrum antibiotics (32).

PENEMS

Faropenem represents an innovative penem antibiotic, designed for oral administration (37). Faropenem is used for the treatment of urinary tract infections (UTIs), respiratory tract infections, skin and skin structure infections, and gynecological infections (38). Its elimination primarily occurs through renal excretion (37). Several research investigations have pointed out that inorganic phosphate transporter 1(NPT1), a transport protein localized in apical membrane of proximal tubular cells, is involved in the active secretion of faropenem (39). There is a possibility of drug interaction when co-administrated with other drugs, such as probenecid (37,39). Probenecid prolongs the exposure duration of faropenem through inhibition of its renal secretion (37, 39).

MONOBACTAMS

Aztreonam

Aztreonam is a monobactam antibiotic. It is indicated for the treatment of UTIs, gonorrhoea, lower respiratory tract infections, bacteraemia/septicaemia, bone and joint infections, gynecological infections (40). Aztreonam elimination is mainly through the kidneys, involving active tubular secretion. Additionally, aztreonam undergoes hepatic metabolism and biliary secretion. Therefore, caution is advised during its administration to patients with renal or hepatic diseases, while dose adjustment is needed in patients with severe renal impairment (40). The pharmacokinetic study showed no major interactions between aztreonam and several antibiotics, such as cephradine, clindamycin, gentamicin, metronidazole or nafcillin (41). On the other hand, antagonism between aztreonam and cefoxitin or imipenem has been described (40). A recently published study described a synergistic interaction between aztreonam and ceftazidime-avibactam. This combination could be an effective strategy for treating infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE), especially in those with high-level resistance levels against carbapenems and/or ceftazidime-avibactam (42). No clinically significant interactions have been observed during concomitant administration of probenecid or furosemide with aztreonam (40). Continuous monitoring and dose adjustment is necessary during concomitant administration of anticoagulants and aztreonam (40).

Carumonam

Carumonam is a new monocyclic beta-lactam antibiotic. It is indicated in the treatment of Gram-negative UTIs. So far, data of interaction potential are scarce. Since the pharmacokinetics of carumonam depend on renal function, in patients with reduced renal function dose adjustment is needed (43).

LIPOGLYCOPEPTIDES

Oritavancin

Oritavancin is a new lipoglycopeptide, approved for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) (8). Oritavancin is a weak inhibitor of CYP2C9 and CYP2C19, and an inducer of CYP3A4 and CYP2D6. Coadministration of oritavancin leads to increased plasma concentration of CYP2C9 (warfarin) and CYP2C19 (omeprazole) substrates and to decreased plasma concentration of CYP3A4 (midazolam) and CYP2D6 (dextromethorphan) substrates (8). Based on this information, caution should be used when administering oritavancin and drugs with a narrow therapeutic index that are metabolized by one of the affected CYP450 enzymes. In addition, oritavancin also has drug-laboratory interactions and may produce falsely elevated results, for example, prothrombin time, INR, activated partial thromboplastin time, and activated clotting time. Therefore, the anticoagulation effect of heparin and warfarin is hard to predict, and alternative anticoagulants should be considered (44).

Dalbavancin

Dalbavancin is also a new representative of lipoglycopeptides, approved for ABSSSIs. Dalbavancin is not metabolized by CYP enzymes, therefore co-administration of CYP substrates, inducers, or inhibitors has no clinically significant effects (8, 44). It is not known if dalbavancin is an inhibitor of transporters or a substrate for hepatic and efflux transporters (8). So far, increased dalbavancin concentration in cases of co-administration with transport inhibitors (verapamil, itraconazole, protease inhibitors) cannot be ruled out. Similarly, increased exposure to transport substrates (statins, digoxin) may be observed after co-administration with dalbavancin (45).

Telavancin

Telavancin is a semisynthetic lipoglycopeptide derivative of vancomycin, approved for treatment of ABSSSIs caused by Gram positive organisms (46). Notably, telavancin is nephrotoxic drug, predominantly eliminated by the kidneys, heightening the risk of interactions with other nephrotoxic drugs and potential accumulation in individuals with renal impairment. It is extensively bound to plasma proteins, so it is possible that DDIs may occur due to the displacement of other highly plasma protein-bound drugs. Additionally, telavancin has been reported to interfere with clotting tests (47). Co-administration of telavancin with aztreonam and piperacillin/tazobactam has shown no observed interactions, indicating that they can be safely used together. Furthermore, CYP450 inducers or inhibitors do not appear to significantly affect telavancin's metabolism (46).

CYCLIC-LIPOPEPTIDE

Daptomycin

Daptomycin is a novel cyclic lipopeptide antibiotic. The co-administration of daptomycin and rifampicin could be a valuable alternative in the treatment of vancomycin-resistant *Enterococcus* (VRE) infections (48). It is approved for the treatment of cSSTIs, infective endocarditis and bacteraemia due to *Staphylococcus aureus* (*S. aureus*) (49). Synergistic interaction is seen with ampicillin/sulbactam, piperacillin/tazobactam, ticarcillin/clavulanate and oxacillin (50). Study represented that daptomycin has a minimal immunomodulatory effect on natural-killer (NK) cells, and synergistic interaction with other immunomodulators such as vitamin E (51). Daptomycin is neither inhibitor nor inducer of CYP450 enzymes, so interactions with drugs metabolized by these enzymes are not expected. No clinically significant interactions were observed between daptomycin and aztreonam, tobramycin nor probenecid. Caution and frequent monitoring are advised during concomitant administration of warfarin and β-hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase inhibitors (50). Daptomycin is primarily cleared by renal filtration, so its increased plasma concentration is observed during concomitant administration with drugs that reduce renal filtration such as non-steroidal anti-inflammatory drugs (NSAID) and cyclooxygenase (COX) 2 inhibitors (50).

PHOSPHONIC ANTIBIOTIC

Fosfomycin IV

Fosfomycin is a bactericidal antibiotic. It is indicated as a therapy for osteomyelitis, cUTIs, nosocomial lower respiratory tract infections, bacterial meningitis, bacteremia and shows qualities in combination with other antibiotics (52). Synergistic interactions were observed during concomitant administration of fosfomycin with linezolid (53), ciprofloxacin (54) and ceftriaxone (55). Potential synergistic activity may occur with daptomycin against methicillin-resistant *S.aureus* (MRSA) infections (56). Clinically significant decreased fosfomycin concentration was observed during concomitant administration of metoclopramide and food (56).

STREPTOGRAMINS

Dalfopristin/quinupristin

Dalfopristin/quinupristin is a broad-spectrum Gram-positive antibacterial belonging to streptogramin class (57). Dalfopristin/quinupristinis indicated for the treatment of severe or life-threatening infections of *staphylococci* or vancomycin-resistant*Enterococcus faecium* (VREF), and skin infections caused by methicillin susceptible *S. aureus* or *Streptococcus pyogenes* (57). It is excreted mainly through feces and lesser through renal excretion as metabolites (57). Dalfopristin/quinupristin inhibits CYP3A4, leading to potential drug interactions (58). Its co-administration with cyclosporine increases dalfopristin/quinupristin plasma concentration (58). It is advisable to closely monitor patients taking drugs metabolized by CYP3A4 concomitantly with dalfopristin/quinupristin (58). *In vitro* studies have shown quinupristin/dalfopristin inhibits the CYP3A4 metabolism of cyclosporin, nifedipine, tamoxifen, midazolam, docetaxel and terfenadine (59). Increased plasma concentration of drugs such as antihistamines, anti-human immunodeficiency virus (HIV) drugs, antineoplastic agents, benzodiazepines, calcium channel blockers, cholesterol-lowering agents, gastrointestinal tract motility agents, immunosuppressive agents, and steroids were observed during concomitant administration with dalfopristin/quinupristin (59).

OXAZOLIDINONE ANTIBIOTICS

Linezolid

Linezolid, an antibiotic belonging to the oxazolidinone class, is registered in RS. Linezolid is indicated for the treatment of VREF infections, complicated and uncomplicated skin and skin structure infections, CAP and nosocomial pneumonia (60). It is a potent OAT1 and OAT3 inhibitor (61). Unlike many other drugs, linezolid does not interfere with the CYP450 system which means that linezolid does not have any interactions with drugs that are metabolized by the CYP system (60). However, recent research has discovered that linezolid's metabolism

can be influenced by two enzymes, cytochrome P450 2J2 and cytochrome P450 4F2, which are not typically associated with drug metabolism (62). Linezolid can be safely combined with aztreonam, ceftazidime, ciprofloxacin, meropenem, gentamicin, amphotericin B, azoles and antiviral drugs (63). However, the *in vitro* study published in 2015 indicated that the bactericidal potential of meropenem was hindered in co-administration with linezolid, diminishing the combined impact of the two drugs on the linezolid-induced bacteriostasis. The authors postulated that as linezolid inhibits protein synthesis and meropenem acts against actively replicating bacteria, the former might halt bacterial growth and thereby neutralize the effect of the latter (64). These findings need further validation, considering that the meropenem–linezolid combination is often employed as empirical antibiotic therapy in healthcare-associated infections. Another *in vitro* study that examined various antibiotic combinations against human macrophage cell lines infected with *Mycobacterium tuberculosis (M. tuberculosis)* demonstrated an antagonistic interaction between linezolid and moxifloxacin. The reasons behind this phenomenon remained unclear (65). Linezolid's blood concentrations are diminished when used alongside rifampicin, and this has garnered increased attention lately due to the risk of antibiotic-resistant bacteria (66, 67). Results from an in *vitro* study showed that linezolid antagonized vancomycin and daptomycin activity (68). A pharmacokinetic interaction study pointed to increased linezolid concentration after co-administration of clarithromycin (69). Linezolid has lipophilic features and excellent tissue penetration, especially into the central nervous system, where it has inhibitory effects on monoamino oxidase (MAO). Therefore, the co-administration of linezolid with drugs that may put patients at risk from MAO inhibition should be closely monitored. Having in mind that linezolid use with serotonergic drugs may lead to serotonergic syndrome, their co-administration is contraindicated (70). Linezolid also interacts with warfarin, leading to decreased INR values (71). Co-administration of linezolid with pseudoephedrine or phenylpropanolamine increases blood pressure (72).

Tedizolid

The history of oxazolidinones provides a vivid illustration of the growing challenges in developing new antimicrobials. Tedizolid phosphate, also known as tedizolid, has joined the ranks of a few antimicrobials that have successfully navigated preclinical and clinical assessments to gain approval in treatment of acute skin and skin structure infections in recent years (73). Tedizolid undergoes minimal hepatic oxidation, and it exerts no detectable influence on the metabolism of CYP450 enzyme substrates, either through inhibition or induction. Moreover, tedizolid did not demonstrate significant hindrance to drug uptake transporters such as OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2 (74). Orally administered tedizolid inhibits BCRP at the intestine level, which may lead to increased concentration of BCRP substrates such as rosuvastatin, imatinib, lapatinib, methotrexate, pitavastatin, sulfasalazine, and topotecan (75). Similar to linezolid, tedizolid is an inhibitor of MAO, however, no clinically significant interactions were observed when co-administered with pseudoephedrine (75). So far, the potential for serotonergic interactions has not been studied.

PLEUROMUTILIN

Lefamulin

Lefamulin is the inaugural systemic antibiotic in the pleuromutilin class (76). Lefamulin exhibits activity against gram-positive and atypical organisms commonly associated with CAP (76, 77). Lefamulin is both a substrate and inhibitor of CYP3A and a substrate of P-glycoprotein *in vitro*(76) and it acts as an inhibitor of OATP1B1, OATP1B3, BCRP, OCT1, and MATE1 transporters. Concomitant administration of lefamulin with amiodarone, Ia and III class antiarrhythmics, antipsychotics, tricyclic antidepressants, fluoroquinolones, macrolides, verapamil, azoles, protease inhibitors and CYP3A4 substrates that prolong the QT interval, is not recommended and should be avoided (78). Concomitant use of lefamulin with moderate or strong CYP3A inducers such as rifampicin, *Hypericum perforatum*, carbamazepine, phenytoin, primidone, can significantly decrease lefamulin plasma concentration (79) and lead to subtherapeutic concentration. On the other hand, concomitant use of strong CYP3a and P-gp inhibitors may lead to increased lefamulin plasma concentration. Therefore, these drug combinations are contraindicated. Co-administration of oral lefamulin with agents metabolised by CYP3A such as alprazolam, alfentanil, ibrutinib, lovastatin, simvastatin, triazolam, vardenafil, and verapamil may result in increased plasma concentrations of these medicinal products (79). Concomitant use of lefamulin with drugs metabolized by CYP2C8 may lead to increased plasma concentration of these medicines (79).

TETRACYCLINE ANTIBIOTICS

Minocycline-IV

Intravenous minocycline, a second-generation semi-synthetic tetracycline, is approved for use in patients with infections due to susceptible strains of Gram-positive and Gram-negative pathogens, such as *A. baumanii* (80). It's important to note that antacids may reduce tetracycline absorption, and concomitant use of isotretinoin and

minocycline should be avoided due to an increased risk of pseudotumor cerebri (80). Additionally, combining tetracycline derivatives with ergot alkaloids heightens the risk of ergotism and acute limb ischemia (81). Concomitant administration of minocycline with penicillin should be avoided. Having in mind that plasma prothrombin activity is depressed by tetracyclines, it is necessary to reduce the dose of concomitant anticoagulants (81). Special caution is needed when minocycline is administered with diuretics or oral contraceptives due to the possibility to aggravate side effects (81).

Omadacycline

Omadacycline is an aminomethylcycline antibiotic designed for the treatment of ABSSSIs and CAP with antibacterial activity against a range of bacteria, including Gram-positive and Gram-negative aerobes, anaerobes, and atypical bacteria (82). In line with other members of the tetracycline family, omadacycline forms non-absorbable chelation complexes by binding with cations (82, 83). It was demonstrated that omadacycline does not act as a substrate, inducer, or inhibitor of the major CYP enzymes (84). Limited data suggest that certain tetracycline antibiotics, including omadacycline, might interfere with warfarin. Therefore, it is recommended to monitor the coagulation profile of patients concomitantly using these medications (82).

Tigecycline

Tigecycline is the first glycylcycline and the first new tetracycline analog marketed after a period of over 40 years (85). Tigecycline is approved for the treatment of cSSTIs with the exclusion of diabetes foot infections, cIAIs, and CAP, while recent studies indicate it may be effective in the treatment of severe *Clostridioides difficille* infection (85). Tigecycline does not inhibit or induce the hepatic CYP450 enzyme system, and it is unlikely to modify the metabolism of drugs metabolized by this system (86). Similarly, substances that induce or inhibit these enzymes are not expected to alter tigecycline clearance. However, tigecycline should be used cautiously in patients with diabetes and patients on oral contraceptive therapy (86). Pharmacokinetics interaction between tigecycline and calcineurin inhibitors, such as cyclosporin A, leads to increased concentration of immunosuppressive agents (87). Co-administration of tigecycline with other antibiotics exhibited either synergy or no interaction effects against the panel of Gram-negative bacteria. No antagonism was observed when tigecycline was co-administrated with piperacillin/tazobactam, ampicillin, amikacin, vancomycin, rifampicin, colistin, polymyxin B, sulbactam, imipenem, ciprofloxacin and levofloxacin. Synergistic interactions were noted with amikacin, ampicillin/sulbactam, piperacillin/tazobactam, minocycline and rifampicin (88). Tigecycline is a substrate for P-gp. Co-administration with P-gp inhibitors, such as cyclosporine and ketoconazole, or P-gp inducers, such as rifampicin, may impact tigecycline's pharmacokinetics (89).

Eravacycline

Eravacycline, a synthetic fluorocycline, shares similarities with tigecycline in terms of mechanism of action, structure and antibacterial spectrum (90). It is approved in several countries for the treatment of cIAIs for adult patients (91). Co-administration of eravacycline and CYP3A4 inducers such as rifampin, phenobarbital, carbamazepine, and phenytoin, led to a reduction in total eravacycline exposure. This data indicates that the dose of eravacycline should be increased when administered concomitantly with potent CYP inducers. On the other hand, the described increased concentration of eravacycline when administered with CYP inhibitors, such as itraconazole, is still clinically unclear (92).

TRIMETHOPRIM-DERIVATIVES

Iclaprim

Iclaprim is a potent and selective inhibitor of bacterial dihydrofolate reductase, and it has exhibited both *in vitro* and *in vivo* efficacy against a range of Gram-positive pathogens, including MRSA, beta-hemolytic *Streptococci* as well as Gram-negative respiratory pathogens (93, 94). Iclaprim is metabolized by CYP3A4 and CYP2C19 enzymes. The interaction potential of iclaprim is not fully investigated. It is not an inhibitor nor inducer of CYP3A4 or CYP2C19 enzymes, suggesting a low potential for clinically significant drug-drug interactions involving these enzymes (93, 94). On the other hand, iclaprim inhibits renal transporters such as OCT1, OCT2 and MATE2-K (93-95).

POLYMYXINS

Colistin

Colistin (polymyxin E) is a lipopeptide antibiotic, registered in RS. It is indicated for the therapy of serious infections caused by aerobic Gram-negative bacteria such as, *Pseudomonas aeruginosa* (*P. aeruginosa*). *A. baumannii*, *K. pneumoniae*, CRE, in patients with limited treatment options (96). *In vitro* studies showed that colistin did not induce the CYP enzymes (97). Co-administration of colistin with other medicines that are potentially neurotoxic (including non-depolarizing neuromuscular blocking agents, aminoglycosides) or nephrotoxic (vancomycin, aminoglycosides, furosemide, calcineurin inhibitors, cephalosporins) should be avoided due to possibility of

summative toxicity (98). *In vitro,* studies have shown that co-administration of colistin and drugs such as macrolides (azithromycin, clarithromycin) and fluoroquinolones (norfloxacin, ciprofloxacin) should be avoided in patients with myasthenia gravis (99). Colistin use may lead to muscle weakness due to reduced acetylcholine release or due to postsynaptic blockade of the acetylcholine receptor (100). Considering colistin's ability to cause muscle toxicity, its co-administration with non-depolarizing muscle relaxants should be used with great caution (98). Several studies have analyzed the synergistic impact of colistin in combination with other antibiotics for the treatment of infectious diseases. For example, colistin and azithromycin have been found to synergistically eliminate Gram-negative bacteria. Simultaneous administration of both drugs could potentially enhance neutrophils' bactericidal capabilities (101). Combinations of colistin with rifampicin and azithromycin have been shown *in vitro* to provide a more potent therapeutic regimen than monotherapy or double combinations against *E. coli* (102). Research has indicated no evidence of antagonism between colistin and antimicrobial agents like gentamicin, ciprofloxacin, piperacillin, and meropenem. Synergy was observed when combining colistin with ceftazidime or aztreonam against *P. aeruginosa* (103). In the context of CRE, combining colistin with another effective *in vitro* antibiotic has proven beneficial. This combination has shown a significant reduction in mortality, particularly in patients with septic shock, high mortality scores, or rapidly fatal underlying conditions (104).

Polymyxin-B

Polymyxin-B, an antibiotic belonging to the polymyxin class, exhibits potent activity against multidrug-resistant Gram-negative bacteria (105). Limited data are available on the specific drug interactions of polymyxin B (105, 106). Coadministration of polymyxin-B with nephrotoxic agents such as aminoglycosides or vancomycin may lead to additive toxicity. Concomitant use of polymyxin B with medications that may potentiate neurotoxicity, such as neuromuscular blocking agents or certain anesthetics, should be used with caution (106).

AMINOGLYCOSIDES

Plazomicin

Plazomicin is a semisynthetic aminoglycoside, with enhanced *in vitro* activity against *Enterobacteriaceae,* encompassing extended-spectrum β-lactamase-producing and carbapenem-resistant isolates (107, 108). It gained approval for the treatment of cUTI, including pyelonephritis caused by susceptible bacteria *E. coli*, *K. pneumoniae*, *Proteus mirabilis* (*P. mirabilis*), *Enterobacter cloacae* (*E. cloacae*) in adult patients (107). Limited information is available on plazomicin's drug interactions with specific agents. Notably, plazomicin is primarily excreted by the kidneys, and there is no evidence of drug metabolism in plasma, liver microsomes, or hepatocytes. *In vitro* studies reveal that plazomicin neither inhibits nor induces the CYP enzymes and is not a substrate for P-gp or BCRP transporters. The concomitant administration of plazomicin with other nephrotoxins may result in additive toxicity (107).

To the best of our knowledge this is the first study that provides prescribers with information about DDIs of reserve antibiotics. Regarding severity level DDIs may be divided into minor, moderate, major or unknown. It is important to emphasize that most DDIs are minor but still can result in health problems and lead to economic burden. The most important sources of information for DDIs are Summary of Product Characteristics (SmPC), DDIs clinical studies, as well as web databases (lexicomp.com, rxlist.com, drugbank.com, medscape.com, drugs.com). Providing prescribers with information regarding antibiotic-drug interactions and education on how to obtain it and how to act on it may be of great impact in the era of combating AMR.

CONCLUSION

The drugs that have high potential for drug-drug interactions are linezolid, colistin, dalfopristin/quinuprstin, lefamulin and oritavancin, all belonging to the reserve group of antibiotics. Special attention should be paid to concomitant use of ceftazidime-avibactam, telavancin, colistin, polymyxin B, plazomicin and drugs that have nephrotoxic potential due to possibility to cause more severe renal impairment. In cases of the reserve antibiotics with limited information regarding interaction potential such as plazomicin, carumonam, iclaprim, further DDIs studies as well as the updating data in the SmPC are needed. Educating clinical staff and supporting the role of clinical pharmacologists regarding the choice of antibiotics based on their interaction potential and optimizing the antibiotic dose may significantly improve the safety and efficacy of pharmacotherapy which is especially important for infections caused by bacterial strains mostly responsible for deaths attributable to AMR.

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CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

Design of the work, B.B.C. and M.B.; preparing the draft of the manuscript and literature review, B.B.C., M.L, M.K.; revision of the manuscript M.B. All authors have read and agreed to the published version of the manuscript.

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LEK-LEK INTERAKCIJE REZERVNIH ANTIBIOTIKA: NARATIVNA REVIJA

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Sažetak

Interakcije lekova su veoma česti razlog za pojavu neželjenih efekata naročito kod dece, starijihi/ili pacijenata sa hroničnim oboljenjima. S obzirom da su antibiotici najčešće korišćeni lekovi potencijalni uticaj interakcija antibiotika sa drugim lekovima na krajnji ishod terapije može biti od kliničkog značaja. Osim toga, interakcije antibiotika sa drugim lekovima mogu uticati i na razvoj antimikrobne rezistencije (AMR) pa je njihovo prepoznavanje od velikog značaja naročito za rezervne antibiotike. Cilj našeg pregleda je analiza potencijalnih interakcija rezervnih antibiotika. Najveći potencijal za stupanje u interakcije imaju linezolid, kolistin, dalfopristin/kvinupristin, lefamulin i oritavancin. Poseban oprez je potreban prilikom istovremene primene antibiotika: ceftazidim-avibaktama, telavancina, kolistina, polimiksina B i plazomicina sa lekovima koji mogu oštetiti bubrežnu funkciju i posledično potencirati nefrotoksične efekte. Takođe, neophodno je obratiti pažnju na rezervne antibiotike za koje nemamo dovoljno informacija o potencijalu za stupanje u interakcije: plazomicin, karumonam, iklaprim. Imajući u vidu da antibiotik-lek interakcije mogu dovesti do izmenjene antimikrobne efikasnosti i/ili bezbednosti, izbor antibiotika mora biti zasnovan na podacima o potencijalnim interakcijama. Kontinuirana edukacija lekara o interakcijama i pravilnom doziranju antibiotika može značajno unaprediti farmakoterapiju i smanjiti rizik za razvoj AMR.

Ključne reči: antibiotik, lek-lek interakcije, rezervni antibiotici, AMR

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