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Antimicrobial drugs involved in potential drug-drug-interactions in cardiosurgical patients

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In hospital setting, antimicrobials are one of the most commonly prescribed drugs. Due to antimicrobial resistance and treatment cost, rational antimicrobial therapy has become a global health priority. One of the measures to control bacterial resistance is a hospital list of antimicrobials with restricted use. Rational antimicrobial therapy includes therapeutic guidelines but often neglects the risk of potential drug-drug interactions (DDI). Patients undergoing complicated surgical procedures are at an increased risk of DDIs. The aim of this study was to analyse the incidence and type of potential clinically significant DDIs of restricted antimicrobial agents in cardiosurgical patients. This prospective study analysed 146 consecutive restricted antimicrobial requests sent to our Central hospital pharmacy for 95 patients. In total, 232 potential clinically significant DDIs were identified and mean number of clinically significant restricted antimicrobial DDIs was 1.6 per request. Potential interactions were identified by *Lexicomp® Lexi-InteractTM Online (Lexi-Comp, Inc., Hudson, USA)* software which categorizes potential DDIs according to clinical significance in five types (A, B, C, D and X). Categories C, D and X are of clinical concern and require interventions (specific therapy monitoring, therapy modification or avoiding combination). Most common were DDIs with ciprofloxacin while interactions of highest level of clinical significance were found with moxifloxacin and linezolid. The most common Anatomical Therapeutic Chemical (ATC) drug groups involved in DDIs with antimicrobials were antithrombotics, antiarrythmics, antidiabetics and potassium. Necessary interventions regarding potential DDIs involving antimicrobial drugs need to be coordinated with the pharmacotherapy treatment priorities.

1. Introduction

Drug-drug interactions (DDIs) are defined as the change in the effect of one drug due to the simultaneous or previous administration of another drug. They represent a frequent pharmacotherapy problem or medication error than can be prevented (Juurlink et al. 2003). DDIs can complicate and compromise the course of treatment, cause undesirable outcomes and increase health care costs (Arnold et al. 2018). DDIs can lead to hospitalization and the extension of an existing one. The consequences of DDIs may manifest differently but usually induce the development of adverse drug reactions or reduce the drug clinical efficacy (Palleria et al. 2013). Certain patient groups such as elderly, patients with chronic diseases, impaired kidney and liver function, patients with comorbidities, patients undergoing a complicated surgical procedure or organ transplant are considered to be at higher risk for DDIs development (Walker and Whittlesea 2007). Cardiosurgical patients are a specific patient group who usually have numerous comorbidities, receive a large number of medications and are often elderly. Furthermore, cardiac surgery is a powerful trigger of a number of immune and other significant processes in the body that can have an impact on the final effect of drugs and the occurrence of side effects (Laffey et al. 2002). In the hospital setting, antimicrobials are one of the most commonly prescribed drugs (Van Der Meer and Gyssens 2001). Due to antimicrobial resistance and treatment cost, the rational use of antimicrobials is one of global health priorities. Rational antimicrobial therapy is predominantly based on therapeutic guidelines and often does not consider potential DDIs. "Multidrug" antimicrobial resistance arguably can have a considerable clinical and economic impact on health care (Howell 2013). Systematic prevention and antimicrobial resistance control are necessary to maintain long-lasting effectiveness of antimicrobial agents for treatment and prophylaxis of infections. Loss of antimicrobial effectiveness represents a threat for patients affected by serious, life-threatening infections in the hospital setting (Allerberger et al. 2009). Antimicrobial stewardship is one of the key interventions necessary to curb further emergence and spread of antimicrobial resistance. In 2017, the World Health Organization (WHO) introduced the Access, Watch, Reserve ("AWaRe") classification of antibiotics in it's Essential Medicines List. The classification is a tool for antibiotic stewardship at a local, national and global level with the aim of reducing antimicrobial resistance. Further, each country and each hospital should make it's own list of restricted antimicrobials considering WHO recommendations and depending on the specificity of local antimicrobial susceptibility or resistance patterns (WHO 2020). As a measure to rationalise antibiotic use and control bacterial resitance, formal protocols such as a list of restricted antimicrobial drugs have been developed in hospital settings (Skrlin et al. 2011). The aim of this study was to analyse the incidence and type of potential clinically significant DDIs of restricted antimicrobial drugs in cardiosurgical patients.

2. Investigations, results and discussion

This prospective study has analysed all requests (146) for restricted antimicrobial drugs made by the Department of Cardiac

Table 1: Patients' baseline characteristics

Characteristic	Values
Number of patients	95
Mean age, years (range)	65.7 (22-85)
Male, n (%)	65 (68.4)
Mean body mass index, kg/m^2 (range)	28.8 (20-41.7)
Number of requests for restricted antimicrobial drug	146
General principles of antimicrobial therapy, n	
Empiric antimicrobial therapy	67
Directed antimicrobial therapy	70
Prophylaxis	1
Continuation of antimicrobial therapy	8
Most frequently isolated microorganism, n	
Escherichia coli	16
Pseudomonas aeruginosa	11
Candida albicans	6
Enterococcus faecalis	6
Klebsiella pneumonie	6
Proteus mirabilis	6
Types of cardiac surgery, n (%)	
Heart valve surgery	51 (45.1)
Coronary artery bypass grafting	33 (29.2)
Aorta surgery	14 (12.4)
Heart transplantation	6 (5.3)
Other	9 (8)
Mean number of diagnosis (range)	5.9 (2-15)
Mean hospital length of stay, days (range)	18.2 (6-134)
Mean number of prescription medications (range)	10.6 (2-19)

and Transplant Surgery in Clinical Hospital Dubrava during a 6 month period. This hospital is a tertiary 600-bed teaching hospital delivering health care to the population of approximately 250 000 inhabitants. Department of Cardiac and Transplant Surgery in Clinical Hospital Dubrava is a part of Unit Dose Drug Distribution System (UDDDS). The requests for the issuance of a restricted antimicrobial agent were obtained through UDDDS. The UDDDS ensures that the clinical pharmacist additionally monitors the prescribed therapy in terms of appropriate indication, pharmaceutical dosage form, dosage and dosing interval. It also provides a screening process for clinically significant DDIs.

Baseline characteristics of study participants are listed in Table 1. Requests for restricted antimicrobial agents were made for 95 patients, most of them male (68.4%). The average patients' age was 65.7 (range 22-85). On average, patients had 5.9 diagnoses according to the International Classification of Diseases (ICD) and 10.6 concomitantly prescribed drugs. On the day the request was sent for the issuance of a restricted antimicrobial drug in central hospital pharmacy, the pharmacotherapy was analysed using *Lexicomp® Lexi-InteractTM Online* (Lexi-Comp, Inc., Hudson, USA) for potential DDI detection.

Overall, we identified 232 potential clinically significant DDIs, which makes on average, 1.6 potential clinically significant DDIs per restricted antimicrobial request. Incidence and types of DDIs were represented in the following order: C (84.1%), D (14.2%) and X (1.7%) (Table 2). Table 2 also shows the most commonly Anatomical Therapeutic Chemical (ATC) drug groups involved in DDIs with restricted antimicrobial agents: antithrombotics, antiarrythmics, antidiabetics and potassium. The most commonly prescribed co-medication was pantoprazole and most commonly implicated ATC drug class was group C (Cardiovascular system). Co-administered drugs are listed in Table 3. In this study, 13 different restricted antimicrobial drugs were required over the defined period. Table 4 shows the number of requests for each antimicrobial drug and the number of potential clinically significant DDIs. Moxifloxacin was identified as an antimicrobial with the highest potential to cause clinically significant interactions (number of interactions/number of requests). The only restricted antifungal agent was fluconazole. Overall, 85.3% of all identified interactions involved fluoroquinolones (95.5% involved ciprofloxacin and 4.5% moxifloxacin) (Table 5). Interactions of highest level of clinical significance (X) were found with moxifloxacin (Table 5) and linezolid (Table 6).

The interaction between ciprofloxacin and acetylsalicylic acid was the most commonly identified potential clinically significant DDI. The buffered form of acetylsalicylic acid can interact with the oral form of fluoroquinolone antibiotics. It can decrease the absorption of oral ciprofloxacin and have an impact on antimicrobial clinical effect and drug resistance. As an intervention, drug dosing interval separation should be considered. Fluoroquinolone antibiotics must be taken at least 2 hours before, or 6 hours after buffered acetylsalicylic acid ingestion, or if it is available, the use of enteric-coated acetylsalicylic acid should be used instead. It is essential to consider consequences of this interaction before switching intravenous to oral ciprofloxacin form. When a patient is clinically stable and able to tolerate oral intake, switching intravenous to oral ciprofloxacin should be considered as soon as possible (Ciprinol 2019). Previous data show that many oral fluoroquinolone-multivalent cation DDIs are of clinical concern (Pitman et al. 2019). Interaction of fluoroquinolones and potassium salts also require drug dosing interval separation, but recommendations for optimal dose separation vary by specific fluoroquinolone. For example, ciprofloxacin should be administered at least 2 hours before or 6 hours after administration of potassium salts while moxifloxacin should be administered at least 4 hours before or 8 hours after administration of potassium salts (Lexicomp 2020). Potassium

Table 2: ATC groups involved in DDIs with restricted antimicrobial drugs

	Total	DDI category		
		C	D	X
Number of DDIs, n (%)	232	195 (84.1)	33 (14.2)	4 (1.7)
Most commonly involved therapeutic groups involved in DDIs with antimicrobial drugs				
B01A Antithrombotic therapy	106	105	1	0
C01B Antiarrhythmics	25	22	1	2
A12B Potassium	18	0	18	0
A10B Blood glucose lowering drugs, excl. insulins	15	15	0	0
A10A Insulins and analogues	10	10	0	0

Abbrevitaions: ATC - Anatomical therapeutic chemical; DDIs - drug-drug interactions

Table 3: Most frequently prescribed co-medications

Drug	Requests, n (%)
Pantoprazole	115 (78.7)
Acetylsalicylic acid	100 (68.5)
Enoxaparin	76 (52.0)
Paracetamol	69 (47.2)
Bisoprolol	67 (45.9)
Furosemide	54 (36.9)
Warfarin	47 (32.2)
Atorvastatin	44 (30.1)
Amlodipine	40 (27.4)
Amiodarone	39 (26.7)
Ramipril	37 (25.3)
Potassium citrate/potassium bicarbonate	28 (19.1)
Potassium chloride	24 (16.4)
Insulin	20 (13.7)
Moxonidine	20 (13.7)
Valsartan	19 (13.0)
Perindopril	18 (12.3)
Lacidipine	17 (11.6)
Hydrochlorothiazide	13 (8.9)
Ipratropium bromide/salbutamol	12 (8.2)
Nebivolol	12 (8.2)
Levothyroxine	11 (7.5)
Metformin	11 (7.5)
Tamsulosin	11 (7.5)
Eplerenon	10 (6.8)
Indapamide	10 (6.8)
Prednisone	10 (6.8)
Urapidil	10 (6.8)
Other	<6.5

Table 4: Number of DDIs including restricted antimicrobial drugs

Antimicrobial drug	Number of DDIs	Number of requests for restricted antimicrobial drug	Potential for DDI (No of DDIs/No of requests)
Amikacin	1	2	0.5
Ampicillin/tazobactam	0	2	0
Cefepime	1	3	0.3
Ceftazidime	0	1	0
Ceftriaxone	1	2	0.5
Ciprofloxacin	189	87	2.2
Fluconazole	16	7	2.3
Imipenem/cilastatin	0	3	0
Linezolid	14	5	2.8
Meropenem	0	18	0
Moxifloxacin	9	2	4.5
Piperacillin/tazobactam	0	4	0
Vancomycin	1	10	0.1
All restricted antimicrobial drugs	**232**	**146**	**1.6**

Abbreviation: DDI – drug drug interaction

salts can chelate with 3-carbonyl and 4-oxo functional groups of fluoroquinolones resulting in inactive antimicrobials. The effect of multivalent cations on the absorption of oral fluoroquinolones is well known. Bioavailability of quinolones under these circumstances depends on the type of fluoroquinolone and the type of cation and can vary greatly (13-67%) (Nix et al. 1989; Shimada et al. 1992; Mallet and Huang 2005; Pitman et al. 2019). Oral fluoroquinolones are an important tool for clinicians, but they must be administered properly to minimize the chances of therapeutic failure, maximize the chances of required clinical outcomes and curb the development of resistance (Pitman et al. 2019).

Concomitant use of ciprofloxacin with vitamin K antagonists may potentiate their anticoagulant effect. The risk of bleeding was significantly increased for warfarin-treated patients who were also treated with a fluoroquinolone, according to the results of separate studies. The extent of the risk varied somewhat among studies according to specific fluoroquinolone and exposure time (Schelleman et al. 2008; Fischer et al. 2010; Baillargeon et al. 2012; Lane et al. 2014). Therefore, recommendation should include frequent monitoring with anticoagulation tests and possible dose adjustment should be considered. Monitoring is especially important during the first few days of concomitant therapy or when the doses of interactans are increased/decreased or shortly after when quinolone antibiotic is discontinued. Precise interfering mechanism for interaction between any fluoroquinolone antibiotic and vitamin K antagonist is not well clarified. Fluoroquinolones can interfere with hepatic metabolism by inhibiting the cytochrome P450 enzyme system. Another possible mechanism is protein binding displacement. Data also suggest that antibacterial interference with enteric flora-mediated vitamin K2 production is another possible mechanism of interaction (Bianco et al. 1992; Israel et al. 1996; Byrd et al. 1999). An additional consideration is the impact of the underlying infection on vitamin K antagonist therapy (Morgan 2009). Infections lead to an increase in circulating concentrations of inflammatory factors like cytokines, glucocorticoids and tumor necrosis factor. Substances released during inflammation and infection elicit a downregulation of some metabolic enzymes, which can mediate the interaction between vitamin K antagonists and other drugs. Even though the contribution of a particular factor is not known, this could explain at least a portion of the observed discrepancy between studies of healthy or non-infected individuals from those who were infected and received a fluoroquinolone (Israel et al. 1996; Byrd et al. 1999; Washington et al. 2007).

Due to recent regulatory restrictions on the use of fluoroquinolones, interactions of fluoroquinolones should be considered in the context of enhanced side effects. Fluoroquinolone have been associated with both hypoglycaemia and hyperglycaemia in both diabetic and nondiabetic patients (Park-Wyllie et al. 2006; Lodise et al. 2007; Aspinall et al. 2009; Chou et al. 2013; Berhe et al. 2019). In July 2018, the Food and Drug Administration (FDA) strengthened it's warning about the risk of hypoglycaemia associated with systemic fluoroquinolone use, particularly for older adults and those with diabetes mellitus (FDA 2018). Therefore, concomitant use of fluoroquinolones and antidiabetics needs to be closely monitored (Catero 2007; Chou et al. 2013). Hypoglycaemia occurs more frequently at the beginning of treatment, while hyperglycaemia is more common and usually seen later during the pharmacotherapy treatment (Graumlich et al. 2005; Mohr et al. 2005).

Moxifloxacin was involved in drug interactions of the highest level of significance (X) in concomitant use with amiodarone. Moxifloxacin is widely used for the treatment of a number of infectious diseases because of it's favourable pharmacological profile and high clinical success rate. However, it is often criticized for it's high risk of QTc interval prolongation and associated *torsades de pointes* (TdP) – malignant cardiac arrhythmias with a potentially fatal outcome. Concomitant use of drugs that prolongs the QTc interval should be

Table 5: Potential DDIs of fluoroquinolones (ciprofloxacin DDIs of category C with < 3 cases are not presented)

Drug - Interactant	Fluoroquinolone	DDI category	N	Potential DDI consequence
Amiodarone	Ciprofloxacin	C	22	QT interval prolongation
	Moxifloxacin	X	2	QT interval prolongation
Acetylsalicylic acid	Ciprofloxacin	C	68	Diminished bioavailability of fluroquinolone
	Moxifloxacin	C	1	Diminished bioavailability of fluroquinolone
Potassium salts	Ciprofloxacin	D	16	Diminished bioavailability of fluroquinolone
	Moxifloxacin	D	2	Diminished bioavailability of fluroquinolone
Sitagliptin	Moxifloxacin	C	2	Hypoglycemia/ hyperglycemia
Insulin	Ciprofloksacin	C	5	Hypoglycemia/ hyperglycemia
	Moxifloxacin	C	2	Hypoglycemia/ hyperglycemia
Metformin	Ciprofloxacin	C	8	Hypoglycemia/ hyperglycemia
Levothyroxine	Ciprofloxacin	C	7	Diminished therapeutic effect of levothyroxine
Naproxen	Ciprofloxacin	C	5	Increased risk of epileptic seizure
Prednisone	Ciprofloxacin	C	3	Increased risk of tendonitis and tendon rupture
Spironolactone	Ciprofloxacin	C	4	Increased arrythmogenic effect of ciprofloxacin
Theophylline	Ciprofloxacin	D	3	Diminshed metabolism of theophylline
Warfarin	Ciprofloxacin	C	32	Increased risk of bleeding
Zolpidem	Ciprofloxacin	D	2	Increased concentration of zolpidem

Abbreviation: DDI – drug-drug interaction

Table 6: Other potential DDIs with restricted antimicrobial drugs (excluding fluoroquinolones)

Antimicrobial drug	Drug - Interactant	DDI category	N	Potential DDI consequence
Fluconazole	Amiodarone	D	1	QT interval prolongation
	Fluvastatin	D	2	Increased serum concentration of fluvastatin
	Atorvastatin	C	1	Increased serum concentration of atorvastatin
	Alprazolam	C	2	Increased serum concentration of alprazolam
	Amlodipine	C	2	Increased serum concentration of CCBs
	Lacidipine	C	3	
	Nifedipine	C	1	
	Cyclosporine	C	1	Increased serum concentration of cyclosporine
	Moxifloxacin	C	1	QT interval prolongation
	Prednisone	C	1	Increased serum concentration of prednisone
	Warfarin	D	1	Increased risk of bleeding
Linezolid	Salbutamol	D	5	Increased blood pressure
	Theophylline	D	1	Increased blood pressure
	Paroxetine	X	1	Serotonin syndrome
	Warfarin	C	3	Increased risk of bleeding
	Insulin	C	3	Increased risk of hypoglicemia
	Metoclopramide	X	1	Increased blood pressure
Amikacin	Furosemide	C	1	Loop diuretics may enhance the adverse/toxic effect of Aminoglycosides
Cefepime	Warfarin	C	1	Cephalosporins may enhance the anticoagulant effect of vitamin K antagonists
Ceftriaxone	Gentamicine	C	1	Cephalosporins (3rd generation) may enhance the nephrotoxic effect of aminoglycosides
Vancomycin	Naproxen	C	1	Increased serum concentrations/toxicity of vancomycin

Abbreviations: DDIs - drug-drug interactions, CCB - calcium channel blocker

avoided. Fluoroquinolones prolong the QT interval by inhibiting cardiac KCNH2 potassium voltage-gated channels (Kang et al. 2001). When safe and effective alternatives are available, fluoroquinolones should be avoided in patients taking other QT-prolonging drugs and patients with long QT syndrome or other significant risk factors for arrhythmia. In our research, amiodarone was the only interactant drug involved in increasing the risk of prolonging QT interval due to DDIs (with moxifloxacin, ciprofloxacin and fluconazole with a different level of significance). Available clinical data suggest that among available fluoroquinolones, moxifloxacin has the highest association with QT interval prolongation, arrhythmia, and cardiovascular mortality, followed by levofloxacin and then ciprofloxacin (Chou et al. 2015: Gorelik et al. 2020.).

Fluroquinolons can be used to treat a wide variety of bacterial infections but their clinical utility is restricted, due to their potential for severe side effects and safety concerns. On 15th November 2018, European Medicines Agency finalised a review of serious, disabling and potentially permanent side effects with quinolone and fluoroquinolone antibiotics. The Committee for Medicinal Products for Human Use (CHMP) has approved recommendations of Pharmacovigilance Risk Assessment Committee (PRAC) that concluded that the use of fluoroquinolones should be restricted due to disabling and potentially permanent side effects involving muscles, tendons or joints and/or the nervous system. It is highlighted that the use of fluoroquinolones should be avoided in patients who previously had serious side effects with a fluoroquinolone or quinolone antibiotic, in elderly, patients with kidney disease and those who had organ transplants because these patients are at greater risk of tendon injury. In 2019, FDA issued a drug safety announcement advising that fluoroquinolone antibiotics can increase the risk for ruptures or tears in the aorta. Certain patients are at increased risk: those with peripheral atherosclerotic vascular diseases, hypertension, or genetic conditions such as Marfan syndrome and Ehlers-Danlos syndrome, as well as elderly patients. In these patients, fluoroquinolones should not be used unless no other treatment options are available. If this is the case, a shorter treatment course (less than 14 days) must be favored (Rawla et al. 2019).

Fluconazole is the first-generation triazole antifungal active against a majority of *Candida* species. This agent is a potent inhibitor for CYP2C9 and moderate inhibitor for CYP3A4 enzyme. Many of the azoles can interact with the CYP450 enzyme system, hence raising the possibility of DDIs (Lass-Flörl 2011). CYP3A4 is the most abundant enzyme in drug metabolism (König and Müller 2013). Most of fluconazole interactions were C interactions (75.0%). Potential clinical consequence of the majority identified interactions with fluconazole were increase of the interacting drug concentration (atorvastatin, fluvastatin, alprazolam, calcium channel blockers, cyclosporine, prednisone). Higher exposure to drug concentration increases the possibility, frequency and the intensity of side effects of the interacting drug. Fluconazole may increase the risk of bleeding in combination with warfarin (Gericke 1993; de Fillete and Michiels 2018). Previous data showed that the risk of gastrointestinal bleeding is two times higher during the administration of these drugs simultaneously. The highest risk of bleeding is 11-15 days after their simultaneous application (Schelleman et al. 2008). It is recommended to initially reduce the dose of warfarin by 10-20% and to increase monitoring of anticoagulant response (Kunze and Trager 1996). Data suggests that larger dose reduction may be necessary, but that the gradual dose reduction is superior to an immediate decrease to the predicted dose requirement. Itraconazole, posaconazole and ketoconazole may have less effect on the bleeding risk than fluconazole (Lexicomp 2020).

Detected linezolid DDIs were C and D level interactions, equally represented. Possible clinical consequences of identified interactions include increase in blood pressure, hypoglycaemia, increased bleeding risk and serotonin syndrome. Linezolid is a synthetic oxazolidinone antimicrobial drug. It is indicated for gram-positive infections for the treatment of bacterial pneumonia, skin and skin structure infections and vancomycin-resistant enterococcal (VRE) infections. Linezolid is also reversible, non-selective monoamine oxidase (MAO) inhibitor (Antal et al. 2001). However, in doses applied as antibacterial therapy it does not exhibit antidepressive effects. In a case report, serotonin toxicity was observed after linezolid co-administration with drugs that change serotonin levels such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, MAO inhibitors and other serotonergic agents such as diphenhydramine, duloxetine, trazodone and venlafaxine (Bolhouis et al. 2011). Prescribing information for linezolid states that concomitant use of SSRIs, MAO inhibitors, tricyclic antidepressants, triptans and dopaminergic drugs with linezolid is contraindicated (Zyvoxid 2019). If a patient is already receiving SSRI therapy and requires urgent treatment with linezolid, SSRI therapy should be stopped promptly upon initiation of linezolid. Monitoring must be done for symptoms of serotonin toxicity for 2 weeks or 24 h after the last dose of linezolid. Therapy with SSRIs can be resumed 24 h after the last dose of linezolid. Some data in high-risk patients suggest a 2-week "washout" period between the discontinuation of SSRIs and the initiation of linezolid (Wigen and Goetz 2002). Concomitant use of linezolid and metoclopramide is contraindicated (X interaction) due to the increased risk of life-threatening hypertension (Reglan 2017). Some data suggest that in the gastrointestinal tract and liver, inhibition of MAO can result in systemic absorption of large amounts of tyramine that can potentially cause life-threatening hypertension (Azzouz and Preuss 2020). High blood pressure is also associated with prolonged use of linezolid. Linezolid is indicated for 10-14 days of therapy. The safety and efficacy of linezolid, when given for >28 days, have not been evaluated in controlled clinical trials (Vazquez et al. 2016; Zyvoxid 2019). Patients with unregulated blood pressure should be monitored closely when using linezolid. Patients with disease-related concerns such as diabetes mellitus, hyperthyroidism, pheochromocytoma and carcinoid syndrome also require close monitoring (Azzouz and Preuss 2020.)

Restricted antimicrobial agents are drugs of special concern. To preserve their effectiveness, it is important to ensure their appropriate and rational use. Knowledge of DDIs is an important parameter of rational pharmacotherapy. Rational use of antimicrobial agent should include DDI risk benefit assessment before restricted antimicrobial drug administration. Patients undergoing complicated surgical procedures are at an increased risk of DDIs and optimising restricted antimicrobial drug use might be difficult. Regarding DDIs interventions, restricted antimicrobials must be cautiously coordinated with established pharmacotherapeutic priorities. Pharmacotherapy problems associated with DDIs need to be timely analysed and presented to clinical audit, as the role of clinical pharmacist in multidisciplinary team is to enhance the quality of prescribing (Jackson et al. 2004). The incidence of DDIs in clinical therapeutics will continue to increase (Lewis 2010). Monitoring, documentation and reporting of clinically significant DDIs is still not on acceptable level for all drug groups, including restricted antimicrobial drugs. Published data on the incidence of potential and/or actual DDIs with restriced antimicrobial drugs are deficient. This paper is a contribution to better defining and understanding of pharmacotherapeutic problems related to DDIs of restricted antimicrobials and their possible consequences. This study has several limitations. This is a single center study that included only specific ward and a specific patient group in which a high potential DDIs incidence of restricted antimicrobial agents was found. Furthermore, we did not include actual clinical outcomes in the analysis. Future research should focus on actual clinical outcomes and include all hospital patients groups to obtain a complete comprehensive insight into the pharmacotherapeutic problems of restricted antimicrobial drugs associated with DDIs. Considering the importance of optimization and rationalization of restricted antimicrobial pharmacotherapy, this paper imposes that risks of potential clinically significant DDIs should be assessed before restricted antimicrobial drug administration.

3. Experimental

This study enrolled consecutive cardiosurgical patients during a 6 month period. Identification of patients' demographic data, laboratory parameters and microbiological data were taken through hospital medical records. Pharmacotherapy data and requests for

restricted antimicrobial agents were obtained through UDDDS in Central hospital pharmacy. Restricted antimicrobial drugs were included according to hospital list of restricted antimicrobial agents, determined by the Drug and Therapeutics Committee (DTC) of the University Hospital Dubrava. Potential DDIs were identified using Lexi-Interact software which categorizes potential interaction according to clinical significance in five groups: (A) no known interaction; (B) specified agents may interact, but there is little or no evidence for clinical concern; (C) the specified agents may interact in clinically significant manner and monitoring of therapy is suggested; (D) the two medications may interact in clinically significant manner and modification of therapy is suggested; (X) contraindicated combination. Descriptive statistical analysis was used to describe patients' demographic data, their therapies and potential DDIs. Proportions were calculated for categorical variables.

Conflicts of interest: None declared.

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