

Povezanost upotrebe antibiotika i infekcija
izazvanih uzročnikom *Clostridioides difficile*
koje su nastale u bolnici tercijernog nivoa
zdravstvene zaštite

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XV Nedelja bolničke kliničke farmakologije 23-24. dec 2023
Sekcija za kliničku farmakologiju „dr Srdjan Djani Markovic“
Srpsko lekarsko drustvo



Uvod

Clostridioides difficile infekcija (CDI) je česta bolnička infekcija (BI) i vodeći je uzrok infektivnih dijareja kod hospitalizovanih pacijenata.

Rizični faktori koji su mnogobrojni, uključuju i prethodno izlaganje antibioticima (AB)

Czepiel, J., et al. *Clostridium difficile* infection: review. *Eur J Clin Microbiol Infect Dis* 2019; **38**, 1211–21.

Brown KA, et al. Antibiotic Prescribing Choices and Their Comparative *C. Difficile* Infection Risks: A Longitudinal Case-Cohort Study. *Clin Infect Dis*. 2021;72:836-44.

Prema riziku da izazovu CDI AB su podeljeni na **visokorizične** antibiotike (cefalosporini, fluorohinoloni, klindamicin, karbapenemi), **srednje rizične** (penicilini, makrolidi, aminoglikozidi, sulfonamidi i trimetoprim) i antibiotike čija primena je povezana sa **niskim rizikom** za ove infekcije (tetraciklini).

Slimings C, Riley TV. Antibiotics and hospital-acquired *Clostridium difficile* infection: update of systematic review and meta-analysis. *J Antimicrob Chemother* 2014;69:881-91.

Raseen Tariq, et al. Low Risk of Primary *Clostridium difficile* Infection With Tetracyclines: A Systematic Review and Metaanalysis. *Clin Infect Diseases* 2018; 66: 514–22.

Klasifikacija antibiotika u Listi esencijalnih lekova Svetske zdravstvene organizacije – **AWaRe**

Access

Amoxicillin
Amoxicillin and clavulanic acid
Ampicillin
Benzathine benzylpenicillin
Benzylpenicillin
Cefalexin or cefazolin
Chloramphenicol
Clindamycin
Cloxacillin
Doxycycline
Gentamicin or amikacin
Metronidazole
Nitrofurantoin
Phenoxyethylpenicillin
Procaine benzylpenicillin
Spectinomycin
Sulfamethoxazole and trimethoprim

Core access antibiotics

Watch

Anti-pseudomonal penicillins with beta-lactamase inhibitor (eg, piperacillin and tazobactam)
Carbapenems or penems (eg, meropenem, imipenem and cilastatin, meropenem)
Cephalosporins, third generation (with or without beta-lactamase inhibitor; eg, cefixime, cefotaxime, ceftazidime, ceftriaxone)
Glycopeptides (eg, teicoplanin, vancomycin)
Macrolides (eg, azithromycin, clarithromycin, erythromycin)
Quinolones and fluoroquinolones (eg, ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin)

also in the

Reserve

Aztreonam
Cephalosporins, fourth generation (eg, cefepime)
Cephalosporins, fifth generation (eg, ceftaroline)
Daptomycin
Fosfomycin (intravenous)
Oxazolidinones (eg, linezolid)
Polymyxins (eg, colistin, polymyxin B)
Tigecycline

- Cilj ispitivanja je bio da se dovede u vezu upotreba antibiotika i gustina incidencije CDI koje su nastale u bolnici tercijernog nivoa zdravstvene zaštite u našoj zemlji

Pacijenti i metode

- U studiju su bili uključeni pacijenti stariji od 18 god. sa inicijalnom epizodom BI od 1. 01. 2011 do 31.12. 2021.
- BI je bila definisana kod bilo kog hospitalizovanog pacijenta sa laboratorijskom potvrdom pozitivnog CD toksina udruženog sa dijarejom (3 puta/dan bez drugih prepoznatih uzroka) ili vizualizacijom pseudomembrana na sigmoidoskopiji, kolonoskopiji, ili histopatološka analiza trećeg dana ili kasnije nakon prijema u bolnicu na dan 1.

Table 2. Trends of antibiotic utilization over an 11-year period in the tertiary university hospital in Serbia according to WHO Access, Watch, and Reserve Classification. Consumption of particular antibiotics is expressed in defined daily doses (DDD) per 100 bed-days (BD).

ATC Code		2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Mann-Kendall Test	
ACCESS GROUP	J01	Total consumption of antibiotics	38.57	38.36	45.08	41.70	43.89	31.94	54.68	47.93	45.66	47.57	56.39	$p = 0.138$
	J01GB06	Amikacin	2.95	3.66	4.15	3.19	4.51	1.34	4.32	4.10	2.06	3.44	3.56	$p = 0.392$
	J01CR02	Amoxicilline + Clavulanic acid	0.16	0.49	0.33	0.29	0.40	0.00	0.24	0.41	0.00	0.15	0.19	$p = 0.083$
	J01CA01	Ampicillin	0.34	1.05	2.29	0.89	1.64	0.25	0.47	0.64	0.21	0.37	0.17	$p = 0.006$
	J01CR01	Ampicillin + Sulbactam	0.07	0.00	0.15	0.00	0.06	0.00	0.06	0.00	0.00	0.00	0.00	$p = 0.035$
	J01CE09	Benzylpenicillin sodium + Procaine benzylpenicillin	1.06	0.70	0.66	0.44	0.34	0.00	0.06	0.04	0.02	0.02	0.01	$p < 0.001$
	J01CE01	Benzylpenicillin sodium (Penicillin G sodium)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.02	0.00	0.00	$p = 0.343$

Table 2. *Cont.*

ATC Code		2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Mann-Kendall Test	
ACCESS GROUP	J01DB04	Cefazolin	0.44	1.20	0.11	0.71	2.21	0.08	1.26	1.15	0.45	3.39	1.11	$p = 1.000$
	J01BA01	Chloramphenicol	0.01	0.00	0.00	0.01	0.03	0.01	0.00	0.00	0.00	0.00	0.00	$p = 0.011$
	J01FF01	Clindamycin	0.29	0.32	0.49	0.56	0.20	0.18	0.51	0.44	0.31	0.18	0.30	$p = 0.139$
	J01GB03	Gentamicin	1.35	1.49	1.47	1.10	1.06	2.81	1.01	0.76	0.64	0.80	0.80	$p = 0.001$
	J01XD01	Metronidazole	5.05	6.77	8.84	7.77	6.43	7.13	9.55	7.50	8.16	9.89	10.31	$p = 0.102$
	J01EE01	Trimethoprim + Sulfamethoxazole	0.40	0.80	0.80	0.67	0.38	0.18	0.48	0.39	0.37	0.45	0.43	$p = 0.042$

J01FA10	Azithromycin	0.01	0.06	0.19	0.38	0.29	0.09	0.31	0.38	0.22	0.98	0.40	$p = 0.073$
J01DC03	Cefuroxime	2.02	4.87	4.04	7.01	3.36	5.59	3.33	3.65	2.16	5.46	1.79	$p = 0.102$
J01DD01	Cefotaxime	0.00	1.01	0.70	0.81	0.34	0.00	0.32	0.13	0.04	0.04	0.00	$p = 0.018$
J01DD09	Ceftazidime	0.44	0.74	0.84	0.24	0.60	0.13	0.61	0.62	0.33	0.61	0.25	$p = 0.139$
J01DD04	Ceftriaxone	15.68	6.29	10.77	8.01	10.60	6.59	15.21	11.81	15.94	6.74	19.14	$p = 0.815$
J01DE01	Cefepime	0.08	0.00	0.00	0.07	0.66	0.01	0.49	0.46	0.35	0.69	0.38	$p = 0.345$
J01MA02	Ciprofloxacin	2.33	1.25	1.12	0.40	0.21	0.19	2.48	0.55	1.70	2.37	3.09	$p = 1.000$
J01FA01	Erythromycin	0.00	0.00	0.02	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00	$p = 0.079$
J01DH03	Ertapenem	0.58	0.56	0.80	1.17	2.22	1.63	1.72	1.52	0.80	1.25	1.21	$p = 0.938$
J01DH51	Imipenem + Cilastatin	0.70	0.99	1.02	1.38	1.14	0.77	1.41	3.03	1.01	1.24	1.95	$p = 0.243$
J01MA12	Levofloxacin	0.00	0.46	0.37	1.75	1.32	0.38	1.52	1.31	3.79	1.09	2.04	$p = 0.274$
J01DH02	Meropenem	1.87	2.77	2.88	1.19	1.71	2.20	3.32	3.76	2.75	3.87	4.14	$p = 0.139$
J01MA14	Moxifloxacin	0.00	0.00	0.00	0.00	0.00	0.00	0.30	0.11	0.00	0.07	0.03	$p = 0.193$
J01CR05	Piperacillin + Tazobactam	0.83	0.76	0.56	1.01	0.85	0.79	1.31	0.83	0.69	0.06	0.41	$p = 0.035$
J01XA02	Teicoplanin	0.07	0.17	0.06	0.07	0.94	0.28	0.08	0.23	0.00	0.00	0.00	$p = 0.115$
J01XA01	Vancomycin	1.78	1.92	2.29	2.21	2.02	1.03	3.31	2.79	3.10	3.11	3.38	$p = 0.102$

ATC Code		2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Mann-Kendall Test
J01	Total consumption of antibiotics	38.57	38.36	45.08	41.70	43.89	31.94	54.68	47.93	45.66	47.57	56.39	$p = 0.138$
RESERVE GROUP	J01XB01 Colistimethate sodium	0.02	0.03	0.08	0.09	0.17	0.15	0.74	0.97	0.46	1.05	1.10	$p = 0.004$
	J01XX08 Linezolid	0.00	0.00	0.01	0.11	0.19	0.10	0.11	0.19	0.07	0.17	0.16	$p = 0.156$
	J01AA12 Tigecycline	0.03	0.02	0.02	0.18	0.00	0.02	0.15	0.14	0.03	0.08	0.03	$p = 0.697$
	ACCESS GROUP	12.12	16.48	19.29	15.63	17.27	11.98	17.96	15.45	12.22	18.68	16.89	$p = 0.697$
	WATCH GROUP	26.39	21.83	25.67	25.70	26.25	19.70	35.73	31.18	32.88	27.59	38.21	$p = 0.243$
	RESERVE GROUP	0.05	0.05	0.11	0.38	0.36	0.26	1.00	1.30	0.56	1.30	1.29	$p = 0.034$

Udeo Access grupe u ukupnoj potrošnji antibiotika je bio od 42.96% in 2013 do 29.95% in 2021.

Udeo Watch grupe u ukupnoj potrošnji antibiotika je bio manji od 56.90% u 2013 do 72% u 2019.

Udeo Reserve grupe u ukupnoj potrošnji antibiotika je bio 0.13% u 2011 i 2012, do 2.73% u 2020.

ATC Code		2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Mann-Kendall Test
J01	Total consumption of antibiotics	38.57	38.36	45.08	41.70	43.89	31.94	54.68	47.93	45.66	47.57	56.39	$p = 0.138$
	ACCESS GROUP	12.12	16.48	19.29	15.63	17.27	11.98	17.96	15.45	12.22	18.68	16.89	$p = 0.697$
	WATCH GROUP	26.39	21.83	25.67	25.70	26.25	19.70	35.73	31.18	32.88	27.59	38.21	$p = 0.243$
	RESERVE GROUP	0.05	0.05	0.11	0.38	0.36	0.26	1.00	1.30	0.56	1.30	1.29	$p = 0.034$

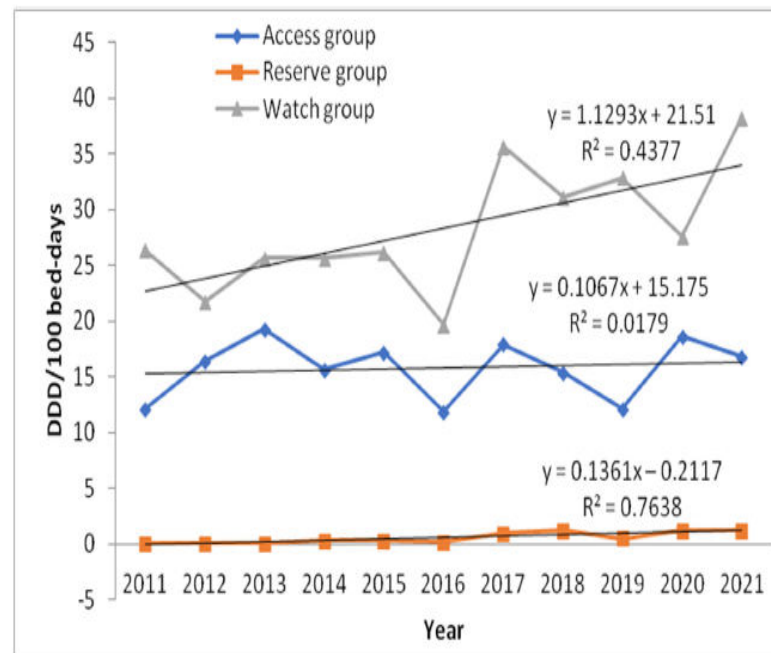


Figure 2. Trend of antibiotic consumption in defined daily doses (DDD) per 100 bed-days according to WHO Access, Watch, and Reserve Classification.

Table 3. Correlation between consumption of particular antibiotics and incidence density (ID) of *Clostridioides difficile* infection in the tertiary university hospital in Serbia, 2011–2021.

ATC Code	Antibiotics		Total Hospital ID of <i>Clostridioides difficile</i>
J01DD09	Ceftazidime	r	-0.439
		p	0.176
J01CE09	Benzylpenicillin + Procaine benzylpenicillin	r	-0.513
		p	0.107
J01FA01	Erythromycin	r	-0.521
		p	0.100
J01GB06	Amikacin	r	-0.545
		p	0.083
J01DD01	Cefotaxime	r	-0.647
		p	0.031
J01CA01	Ampicillin	r	-0.773
		p	0.005
J01CR02	Amoxicilline + clavulanic acid	r	-0.821
		p	0.002

Table 4. The consumption of antibiotics according to the risk for *Clostridioides difficile* infection in defined daily doses (DDD) per 100 bed-days (BD) from 2011 to 2021.

		2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Mann-Kendall Test
High-risk antibiotics	First-generation cephalosporins	0.44	1.20	0.11	0.71	2.21	0.08	1.26	1.15	0.45	3.39	1.11	$p = 1.000$
	Second-generation cephalosporins	2.02	4.87	4.04	7.01	3.36	5.59	3.33	3.65	2.16	5.46	1.79	$p = 0.102$
	Third-generation cephalosporins	16.11	8.05	12.32	9.06	11.54	6.73	16.15	12.56	16.32	7.40	19.39	$p = 0.938$
	Fourth-generation cephalosporins	0.08	0.00	0.00	0.07	0.66	0.01	0.49	0.46	0.35	0.69	0.38	$p = 0.345$
	Carbapenems	3.15	4.32	4.71	3.73	5.07	4.61	6.45	8.31	4.56	6.36	7.30	$p = 0.139$
	Fluoroquinolones	2.33	1.71	1.49	2.15	1.52	0.57	4.30	1.97	5.49	3.53	5.16	$p = 0.586$
	Clindamycin	0.29	0.32	0.49	0.56	0.20	0.18	0.51	0.44	0.31	0.18	0.30	$p = 0.139$
Medium-risk antibiotics	Penicillins	24.64	25.24	26.43	24.62	25.45	23.25	23.83	24.11	23.24	23.54	23.37	$p = 0.002$
	Aminoglycosides	4.30	5.16	5.62	4.28	5.56	4.15	5.33	4.86	2.70	4.23	4.36	$p = 0.052$
	Macrolides	0.01	0.06	0.20	0.38	0.30	0.09	0.31	0.38	0.22	0.98	0.40	$p = 0.086$
	Sulfamethoxazole and Trimethoprim	0.40	0.80	0.80	0.67	0.38	0.18	0.48	0.39	0.37	0.45	0.43	$p = 0.042$
Low-risk antibiotics	Tigecycline	0.03	0.02	0.02	0.18	0.00	0.02	0.15	0.14	0.03	0.08	0.03	$p = 0.697$

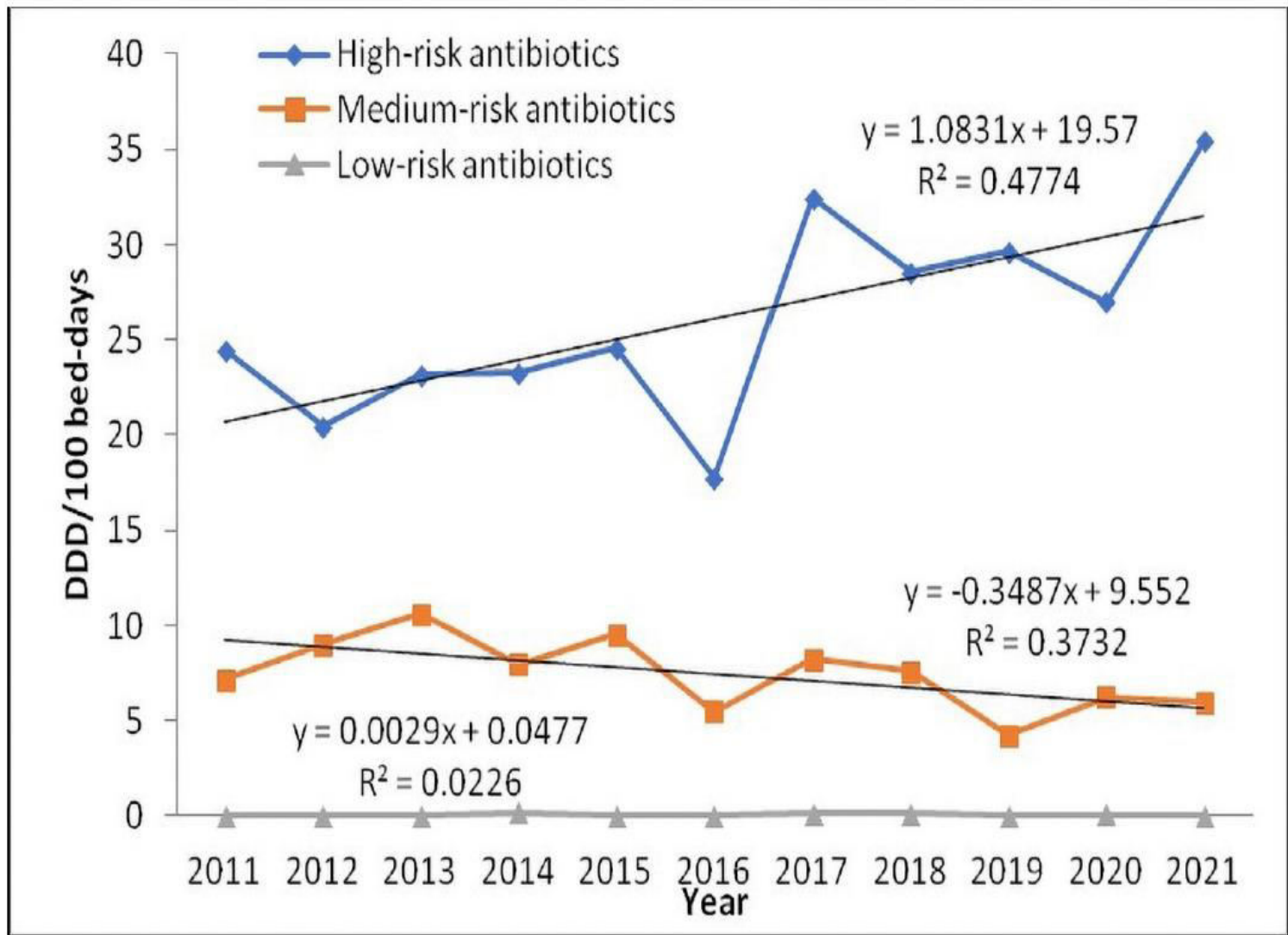


Figure 3. Trend in antibiotic consumption in defined daily doses (DDD) per 100 bed-days from 2011 to 2021 based on the risk of *Clostridium difficile* infection. High-risk antibiotics, Mann-Kendall test; $p = 0.186$; Medium-risk antibiotics, Mann-Kendall test; $p = 0.010$; Low-risk antibiotics, Mann-Kendall test; $p = 0.873$.

Table 5. Correlation between consumption of antibiotics classified according to the WHO Access, Watch, and Reserve classifications and the risk of *Clostridioides difficile* infection with the incidence density (ID) of *Clostridioides difficile* in the Serbian tertiary university hospital from 2011 to 2021.

	ID of <i>Clostridioides difficile</i>	
Access group of antibiotics	r	-0.275
	p	0.414
Reserve group of antibiotics	r	-0.037
	p	0.915
Watch group of antibiotics	r	0.261
	p	0.438
High-risk antibiotics	r	0.220
	p	0.516
Medium-risk antibiotics	r	-0.677
	p	0.022
Low-risk antibiotics	r	-0.160
	p	0.638
TOTAL ANTIBIOTIC CONSUMPTION	r	0.055
	p	0.873

ZAKLJUČCI

- Učestalost BI izazvane CD se nije značajno menjala u posmatranom 10. god. periodu, kao ni potrošnja AB u celini
- Potrošnja srednje rizičnih antibiotika (penicilini, makrolidi, aminoglikozidi) je pokazala značajno negativnu korelaciju sa učestalošću BI izazvane CD
- Potrošnja AB koji pripadaju rezervnoj grupi je imala značajan trend povećanja u vremenu
- Potreban je dalji rad na racionalizaciji propisivanja AB u bolničkim uslovima