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Prevalence of antimicrobial resistance in *Campylobacter* spp.: A review of the literature

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REVIEW ARTICLE

ABSTRACT

Campylobacter spp. are commensal organisms in the intestinal tract of food producing and companion animals. There is an increasing trend of human campylobacteriosis worldwide, including complicated cases that request treatment by antibiotics. Prevalence of resistance continually increases, especially to fluoroquinolones and tetracyclines. There are many reports on multiresistant strains of *Campylobacter* spp.

In this work we present the available information about the prevalence and antimicrobial resistance of *Campylobacter* spp. worldwide, as well as studies from Serbia published in last two decades. *Campylobacter* strains isolated from animal samples in Serbia showed increased prevalence of antimicrobial resistance to all clinically relevant antibiotics. Preliminary data (2014–2019) from Reference laboratory for *Campylobacter* and *Helicobacter* at the Institute of Public Health of Niš, Serbia show high resistance rates to ciprofloxacin (90%) and to tetracycline (50%) but low resistance to erythromycin (<5%) in human *Campylobacter* isolates.

KEYWORDS

Campylobacter jejuni, ***Campylobacter coli***, **antibiotics**, **prevalence**, **resistance**, **Serbian**

INTRODUCTION

Campylobacteriosis is a food borne disease and one of the most prevalent zoonosis [1–3]. An increasing trend of human campylobacteriosis is recorded in the whole world. *Campylobacter* is the most frequently reported cause of zoonotic diseases in European Union [4]. The overall incidence of 64.8 cases per 100,000 population was reported in EU countries in 2017 [3]. It was the second most common food borne illness in the USA [5]. Among 31 species belonging to the genus *Campylobacter*, thermophilic species, as they grow preferentially at 42 °C – *Campylobacter jejuni and C. coli* are causative agents of human infections. These species are commensal organisms in the intestinal tract of various animals, especially in ruminants, swine and poultry. The prevalence of species involved in human infections are 90% for *C. jejuni* and 10% for *Campylobacter coli* [2]. *Campylobacter* is usually indirectly transmitted to humans through the consumption of food contaminated by feces of infected animals. Contamination occurs during meat processing. Sporadic cases of campylobacteriosis in humans often develop after consumption of undercooked poultry meat. Outbreaks are primarily related to ingestion of raw milk or dairy products [1]. Retail poultry may be highly contaminated by *Campylobacter* spp. and it is recognized as a public health challenge all over the world [6]. Recent outbreaks in USA were related to contact with *Campylobacter*-infected puppies. Therefore, dog breeding has emerged as an additional risk factor for human campylobacteriosis [1].

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ANTIBIOTIC TREATMENT OF HUMAN CAMPYLOBACTERIOSIS

Human campylobacteriosis is a self-limiting gastroenteritis with diarrhoea that resolves spontaneously, without therapy, on an average of five days. However, the number of long-term campylobacteriosis increases with consequent extra-intestinal complications. The most dangerous are septicemia, meningitis, and arthritis [7]. Such cases require antibiotic therapy. According to the recommendations of European Committee on Antimicrobial Susceptibility Testing – EUCAST [8] the choice of antibiotics for the treatment of campylobacteriosis is narrowed only to tetracyclines, macrolides (azithromycin, erythromycin and clarithromycin) and fluoroquinolones (ciprofloxacin) [8, 9]. Macrolides are antimicrobials of the first choice [1]. Until recently, drugs of the first choice were fluoroquinolones and tetracyclines [7], but faced to raising trend of resistance to these antimicrobials, the recommendations were changed. In extremely severe forms of *Campylobacter* infections, aminoglycosides and imipenem (carbapenems) are recommended [1, 7].

For *in vitro* studies of the susceptibility of *Campylobacter* to these antibiotics, EUCAST provided precise standards for method performance and interpretation of results [8]. Unlike EUCAST that established standards for the categorization of *Campylobacter* susceptibility to macrolides, fluoroquinolones and tetracyclines, Antibiogram Committee of the French Society for Microbiology (CA-SFM) provided a standard prescription for *in vitro* susceptibility testing of *C. jejuni* and *C. coli* using disk diffusion method and dilution method in agar for tetracycline, fluoroquinolones, macrolides, ampicillin and amoxicillin with clavulanic acid. In addition, CA-SFM recommended the use of gentamicin and ertapenem [10]. However, the cut-off values of the zones of inhibition and the values of the minimum inhibitory concentration (MIC) are different depending on the applied recommendations.

PREVALENCE OF ANTIMICROBIAL RESISTANCE

Campylobacter has been exposed to antibiotics used in food producing animals, companion animals and humans. The organism developed various antibiotic resistance mechanisms. Therefore, antimicrobial resistance of *Campylobacter* species is increasing.

In EU, obtained data for *C. jejuni* and *C. coli* of human and animal origin in 2017–2018, showed very high to extremely high levels of resistance to fluoroquinolones. In strains from human samples average for ciprofloxacin resistance was 59.3 and 65.2% for *C. jejuni* and *C. coli*, respectively. Resistance to erythromycin was detected at low levels in *C. jejuni* from humans and animals, but higher levels in *C. coli* isolates. The proportion of human *C. jejuni* isolates resistant to erythromycin was low (1.8%), but significantly higher in *C. coli* (14.3%). High (47.2%) and extremely high (71.3%) proportions of resistance to tetracycline were observed in *C. jejuni* and *C. coli*, respectively [11].

In *Campylobacter* isolates recovered from meat samples of broilers and turkeys collected in 2018, resistance was higher in *C. coli* than in *C. jejuni*. Among *C. jejuni* and *C. coli* isolates recovered from poultry meat, the highest levels of resistance were noted for ciprofloxacin, nalidixic acid and tetracycline (54–83%). Tetracycline resistance ranged from high to very high within each of the animal origins – the highest levels of resistance were noted in *C. coli* isolates recovered from broilers (61.4%) and *C. jejuni* from turkeys (56.1%). Among *C. jejuni* from poultry and calves, erythromycin resistance was either not found or detected at very low to moderate levels (1.1, 1.3 and 1.2% in turkeys, broilers and calves, respectively). Generally, erythromycin resistance was observed at higher levels in *C. coli* isolates recovered from fattening pigs (15.6%) [11].

Very high ciprofloxacin resistance was reported worldwide. Sproston et al. [2] summarized results of 30 studies from various geographical regions. The highest resistance proportion of *Campylobacter* isolated from humans (infant feces) was found in Peru (87% *C. jejuni*, 91.3% *C. coli*) and China (86.7% *C. jejuni*), from broilers in China (99.2–100% *C. jejuni* and *C. coli*) and from pigs in China (97% *C. coli*). The highest ciprofloxacin resistance in broilers and chicken meat corresponds to the extremely high levels recorded in human isolates between 2003 and 2010. *C. jejuni* isolates from broiler chicken meat showed fluoroquinolone resistance in 100% strains in Latvia and 84.6% in Lithuania [12].

In the U.S. a recent CDC report revealed a rising trend of ciprofloxacin-resistant *Campylobacter* for the past two decades with 29% resistance rate in 2017. In Australia, fluoroquinolones have never been used in poultry, but the rate of fluoroquinolone resistance in *C. jejuni* isolates of poultry origin has risen to almost 15% [1].

In a world-wide meta-analysis on antimicrobial resistance of thermotolerant *Campylobacter* species [13], isolates showed different prevalence depending on the continent. Studies from Latin America presented the highest prevalence of resistance to almost all the antimicrobials, except for erythromycin and streptomycin. The highest prevalence of *Campylobacter* isolates from humans resistant to tetracycline was recorded in Asia and the lowest in Africa. Prevalence of resistance to erythromycin in human isolates did not show any difference regarding the continent, but in broiler isolates, prevalence was higher in those from Africa and Asia and lower in Europe and Latin America.

In recent years, there are many reports on multidrug resistant strains of *Campylobacter*. In an Italian study, among 176 *C. jejuni* and 41 *C. coli* isolates 49.4% *C. jejuni* were resistant to two antimicrobials, while 36.6% *C. coli* strains were resistant to two and at the same rate (36.6%) to three drugs. High percentage of *Campylobacter* isolates was resistant to ciprofloxacin and tetracycline (48% C. *jejuni* and 41% *C. coli*) and 29% Italian human *C. coli* strains were resistant to ciprofloxacin, tetracycline and erythromycin [14].

The study on *Campylobacter* resistance of 989 *C. jejuni* and 1991 *C. coli* isolates from broiler chickens and swine in five Chinese provinces during 2008–2014 revealed high prevalence of multidrug resistance, including shift of the dominant species from *C. jejuni* to *C. coli* in chicken, with increased prevalence of macrolide-resistant *C. coli* [15]. Another Chinese study on *Campylobacter* species isolated from broilers in live bird markets in Shangai, showed that more than 96% strains were resistant to fluoroquinolones and tetracyclines. High prevalence of macrolide resistance (erythromycin 84%, azithromycin 80.8%) was observed in *C. coli*, but not in *C. jejuni* (erythromycin 6.0%, azithromycin 2.4%) [16]. Multidrug resistance strains of *Campylobacter* were isolated from ducks in Chinese slaughterhouse (75.9%) [17], retail meat in Pakistan (90.4%) [18], chicken samples in Jordan (100%) [19], chicken carcasses in Poland during 2014–2018 (20.6% *C. jejuni* and 25.1% *C. coli* were multiresistant) [20].

Macrolides are antimicrobials of the first choice in clinical treatment of *Campylobacter* infections. So far, resistance of *Campylobacter* species to erythromycin and other macrolides has been low, especially in *C. jejuni*. Data from the integrative report of the National Antimicrobial Resistance Monitoring System (NARMS) in U.S. showed that the prevalence of erythromycin resistance in *C. jejuni* has remained below 4% in human and chicken isolates. However, erythromycin resistance in *C. coli* derived from humans more than tripled in 2014 compared to 2011 (10.3 versus 2.7%) and more than doubled in retail chicken isolates in the same time frame (11.4 versus 5.2%) [21]. Antimicrobial resistance trend for macrolides shows similar pattern in Europe and USA.

According to the results of 283 scientific papers in meta-analysis, Signorini et al. [13] stated that *C. coli* isolates presented higher prevalence of antimicrobial resistance to most of the antimicrobials comparing to *C. jejuni*. Thermotolerant *Campylobacter* strains isolated from humans did not show differences in the prevalence of antimicrobial resistance, except that *C. coli* exhibited higher resistance to erythromycin than *C. jejuni*.

STUDIES ON *CAMPYLOBACTER* IN SERBIA

Serbia is located in South-East Europe and it is not a member state of EU. The surveillance of enteritis caused by *C. coli/jejuni* has been carried out since 1997. Reporting of *C. coli/jejuni* in human samples has been performed since 2005. Average annual incidence of enteritis caused by *Campylobacter* in Serbia was 5.30 per 100.000 population from 2005 to 2017. It shows increasing trend in our country [3]. Reference laboratory for *Campylobacter* and *Helicobacter* at the Institute of Public Health of Niš registered on average 1,577 *Campylobacter* isolates annually, from 2012–2019 (www.izjn, access date May 19, 2021). Regarding the highest risk of infection originating from consuming poultry, monitoring of *Campylobacter* in poultry carcasses has been mandatory since January 1, 2019 in Serbia [3]. In region of Vojvodina, *C. jejuni/coli* was identified at farm level in 73.3% of poultry samples, 66.6% calve samples and 58.3% pig samples of already ill or suspected cases [3].

Several authors examined antimicrobial resistance of *Campylobacter* species isolated from food-producing animals and human samples during last two decades. Results of the studies are showed in Table 1.

Campylobacter strains isolated from animal samples over last two decades showed increasing prevalence of antimicrobial resistance to all clinically relevant antibiotics: ciprofloxacin, tetracycline, nalidixic acid, including erythromycin and gentamycin (Table 1). Recent publication on *Campylobacter* resistance isolated from human samples is lacking, although preliminary data from Reference laboratory for *Campylobacter* and *Helicobacter* at the Institute of Public Health of Niš, show that resistance to ciprofloxacin ranged between 80 and 90%, and to tetracycline between 20

Table 1. Prevalence of resistant *Campylobacter* spp. in Serbia from 2007 to 2020

Publication	Samples	Number of strains	Method	Erythro mycin	Genta mycin	Tetra cycline	Cipro floxacin	Nalidixic acid	Chloram phenicol
Ivanović et al. 2007 [24]	pigs (2007)	18	ADA*	0	NE***	100%	NE	NE	NE
	human feces (1998)	105	DDM** DDM	3%	9%	0	NE	NE	0
Miljković-Selimović et al. 2009 [25]	human feces	131	ADA	2.4%	0	9.9%	29.8%	33.3%	0
Ristić et al. 2009 [26]	human feces	50	DDM	2%	2%	2%	44%	44%	4%
Petrović et al. 2011 [27]	poultry carcasses		ADA	7.59%	5.69%	NE	46.20%	NE	0
	pig carcasses		DDM	0	0	NE	0	NE	0
Tambur et al. 2009 [28]	broiler chickens	16	E-test	12.5%	NE	62.5%	56.2%	NE	NE
Tambur et al. 2011 [29]	Pigs	15	E-test DDM	40%			26.7%		
Jovanović 2020 [6]	poultry carcasses	89	DDM E – test	39.33% 37.04%	13.48% 11.11%	60.67% 59.26%	59.55% 48.15%	67.42% 55.56%	NE

*ADA – agar dilution method.
**DDM – disk diffusion method.
***NE – not examined.

and 50% in period 2014–2019. In the same time, resistance to erythromycin was still low (<5%) (www.izjn, access date May 19, 2021).

CONCLUSIONS

Recent reports worldwide showed alarming situation regarding the prevalence of antimicrobial resistance of *Campylobacter*. Currently, there are many research efforts in various approaches to control *Campylobacter*: application of prebiotics and probiotics, as well as fatty acids, in order to prevent and reduce *Campylobacter* colonization in animals and humans, bacteriocins as a potential alternative for antibiotics, phage therapy and immunization [1]. However, it is still early to apply any of these methods widely. It is well known that antimicrobial agents have been used in growth promotion and disease control in food-producing animals, especially poultry [13]. From 2006, all growth promoters have been banned from European agriculture by Regulation (EC) No 1831/2003 of the European Parliament. In Serbia, the complete feed for animals must not contain antibiotics and sulfonamides (Roolbook on the Quality of Animal Feed/Pravilnik o kvalitetu hrane za životinje, 2010). However, the use of antibiotics as growth promoters is still a practice in many countries. The strategy to use antibiotics in animals, which are not used in humans (e.g. monensin, salinomycin, tylosin, spiramycin, avilamycin, avoparcin, ardacin, olaquindox and carbadox) did not decrease the risk of antimicrobial resistance to clinically important antimicrobials, because of chemical similarity and capability to produce cross-resistance [22]. In addition, resistance persists or even increase in the absence of antibiotic usage, especially to fluoroquinolones [1]. In France, the EcoAntibio plans (EcoAntibio 1, 2012–2017 and EcoAntibio 2, 2017–2021) are a public policy set up by the French Ministry of Agriculture and Food with the goal to reduce use of antimicrobials among animals and to diminish antimicrobial resistance. Impact of the measures was evaluated in the study by Perrin-Guyomard et al. 2020 [23]. Tremendous decrease in the exposure to fluoroquinolones of poultry and pigs from 2011 to 2018 was noted. However, the results observed for fluoroquinolone resistance in bacteria from poultry and pigs in France did not follow the trend in fluoroquinolone consumption. Positive effect was on bacteria from diseased animals. For these strains, resistance to fluoroquinolones showed a clear decrease. The authors concluded that responsibility in use of fluoroquinolones must be maintained and strongly encouraged [23].

Antimicrobial resistance of *Campylobacter* strains isolated from animals in Serbia follows the increasing trend as in other European countries. Legislation is set according to the European recommendations, but monitoring and control of antimicrobial usage should be improved. Preliminary data on *Campylobacter* resistance of human isolates show similar trends as in other European countries and detailed research will be perform in the future study.

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