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PLASMID MEDIATED RESISTANCE TO QUINOLONES IN *SALMONELLA*

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Abstracts

Plasmid mediated resistance to quinolones in *Salmonella enterica* is briefly presented. World wide spread of *qnr* determinants is evident, indicating the necessity for prudent use of antimicrobials in human and veterinary medicine. In discovering plasmid mediated resistance to quinolones antimicrobial resistance monitoring for β-lactam antibiotics is helpful, since their target genes frequently coexist in plasmid. Nevertheless, 100% reliable method for screening of *qnr* determinants has not been discovered. The finding of *qnr* genes and other determinants from the large collection of *Salmonella* isolates in respective national laboratories, in several countries is described. Individual cases of *qnr* positive *Salmonella* from patients, reported in recent years, are also presented.

Key words: plasmid mediated resistance, resistance to quinolones, *Salmonella*

QNR DETERMINANTE KOD SALMONELA

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Kratak sadržaj

U radu je ukratko opisana plazmidski prenosiva rezistencija na hinolone kod *Salmonella* enterica. Zahvaljujući rasprostranjenosti *qnr* determinanti u svetu, neophodna je pažljiva upotreba antibiotika u humanoj i veterinarskoj medicini. Kako bi utvrdili plazmidski prenosivu rezistenciju, potrebno je da se na *qnr* i ostale determinante testiraju izolati koji su rezisteni na beta laktame, zato što su njihovi ciljni geni često nađeni zajedno na plazmidu. Ipak, 100% siguran metod za detekciju *qnr* gena za sada nije pronađen. U radu je opisan nalaz *qnr* i drugih plazmidski prenosivih gena koji dovode do rezistencije na hinolone, u velikim kolekcijama izolata salmonela iz Nacionalnih laboratarija u nekoliko zemalja. Takođe su opisani individualni slučajevi infekcije *qnr*+ salmonelama kod pacijenata, u zadnjih par godina.

Ključne reči: plazmidski prenosiva rezistencija, rezistencija na hinolone, *Salmonella*

INTRODUCTION

A brief description of genetic models in resistance transfer was published recently in our Institute (Velhner et al., 2010). Since quinolones are the most commonly used drugs for animals in our country, resistance among enterobacteria is expected. When exposed to quinolones, bacteria respond to the new environment utilizing different defense mechanisms. The target enzyme for quinolones is termed gyrase and it is indispensable for bacterial replication. This enzyme changes the topography of the DNA by unwrapping and breaking DNA strand to prepare the chromosomal material for replication. Gyrase also participates in DNA "packaging" once replication takes place. Quinolones bind to the enzyme precluding the replication and ending the bacterial life cycle. If mutations occur at the quinolone resistance determining region (QRDR) of the genes coding for gyrase subunits, quinolones cannot bind to the DNA/gyrase complex (Robicsek et al., 2006c) resulting in uninterrupted replication and survival of resistant bacteria. Until the mid 1990s it was thou-

ght that such genetic events are the only mechanism of resistance to quinolones, beside intrinsically related inducible mechanisms, mediated by porin loss and overexpression of efflux pump. However, Martinez Martinez and colleagues discovered a novel *qnr* determinant conferring resistance to quinolones from a clinical isolate of *Klebsiella pneumoniae* in 1994 in the USA. The gene marked *qnrA* was located on a transferable plasmid pMG252 (Martinez Martinez et al., 1998). There is an opinion that *qnr* increases possibility of mutant survival. It is often present in multiple resistant bacteria and subsequently it could facilitate their spread in the environment (Hopkins et al., 2005; Tran and Jacoby, 2002; Robicsek et al., 2006b).

The *qnr*

After the discovery of plasmid mediated resistance to quinolones, the research on biochemical composition and the mode of action of the Qnr protein has started. A transformed referent *E .coli* J53 laboratory strain with the plasmid pMG252 was analyzed by Tran and Jacoby (2002). Utilizing cloning and nucleotide sequence analysis of the transformants, it was discovered that Qnr protein had a nature of pentapeptide repeat family and that it was composed of 218 amino acids. These proteins represent tandem five residue repeats A(D/N)LXX where X could be any amino acid. They have diverse activities and could be found in many bacteria species. The Qnr protein is binding to gyrase holoenzyme and gyrase subunits GyrA and GyrB at the very beginning of the enzyme/DNA interaction. Subsequently, its activity does not require conformational changes of the molecule that occurs if the enzyme binds to ATP, DNA or ciprofloxacin (Tran and Jacoby, 2002; Tran et al., 2005). Several *qnr* determinants have been recognized. The best studied is *qnrA*, but beside it *qnrB* was found in *Citrobacter koseri*, *Escherichia coli*, *Enterobacter cloacae* and *Klebsiella pneumoniae*. The *qnrS* was found for the first time in *Shigela flexneri* isolated in Japan (rev by Nordmann and Poirel, 2005; Jacoby et al., 2006). Amino acid compositions of *qnr* proteins (QnrA, QnrB and QnrS) are different. Their origin is not known, but the sequence derives from the chromosome (Nordmann and Poirel, 2005, Robicsek et al., 2006c). Since they are quite rare among *Salmonella*, intensive survey is needed to find *qnr* determinants. Subsequently, a screening with the participation of a number of public health laboratories in the USA, lead to the discovery of *qnrB* and *qnrS* genes. They were found in isolates of non-typhi *Salmonella* from humans. The strains were collected during the years 1996 to 2003. The MIC to ciprofloxacin was determined for 12.253 isolates of *Salmonella enterica*, and it was estimated that only 0.1% were ciprofloxacin resistant. Among 233 isolates (MIC to CIP

≥0.06 μg/mL), 10 isolates were *qnr* positive and carried *qnrB2*, *qnrB5*, *qnrS1* and *qnrS2* genes. The isolates had low level resistance to CIP (MIC 0.25 to 0.5 μg/mL). This was also the first report on *qnr* from the USA (Gay et al., 2006). The *qnrD* gene was first discovered by Cavaco and coworkers in 2009 (Cavaco et al., 2009). It was identified in *S*. Bovismorbificans and *S*. Kentucky in human isolates from Henan province in China.

Another plasmid mediated resistance determinant termed *aac-6`-lb-cr*, interactive to aminoglycoside antibiotics, also reducing activity of fluoroquinolones, was discovered in clinical isolates of *E. coli* from a hospital in Shangai-China (Robicsek et al., 2006a). A *qepA* efflux pump gene from a plasmid, mediating resistance to fluoroquinolones was described in *E. coli* by Yamane et al. (2007). It is postulated that *qepA* gene was transferred to *E. coli* from microbes that produce compound or metabolites that are similar to fluoroquionolone. Such microbes may have built the active transporters, to extrude antimicrobials from the cell. It is also possible that the *qepA* gene, rich in GC content, was dissected and integrated to plasmids as a chromosomal fragment from actinomycetes. This observation is also made for the *rmtB* gene, responsible in mediating resistance to aminoglycoside. In *qep* positive *E. coli* the MIC to ciprofloxacin was 0.125μg/mL for norfloxacin it was 1 μg/mL and for enrofloxacin it was 0.25 μg/mL.

The prevalence of *qnr* genes in humans, food and animals

The possibility of worldwide dissemination of *qnr* determinants is of great concern, because plasmid mediated resistance can be easily spread among enterobacteria. Since the overuse of antibiotics facilitates survival and transfer of mobile genetic elements among bacteria, prudent use of antibiotics in humans and animals is necessary.

Research on prevalence and distribution of the *qnr* gene is important. The *qnr* determinants were found in *Enterobacteriaceae* from humans, food and food producing animals, most often if MIC to CIP and NAL is increased, but bellow current CLSI breakpoint. It was also evident that *qnr* protein facilitates resistance development to quinolones. The *qnr* genes have been found in multiple resistant bacteria and in some cases its appearance was connected with resistance to extended-spectrum β-lactamases (ESBLs) (Poirel et al., 2005; Robicsek et al., 2006b; Cavaco et al., 2009). Susceptibility to NAL and intermediate resistance to CIP in *Salmonella enterica* is also proposed for the screening of *qnr* determinants by Hopkins et al. (2007). Conferring nontypical quinolone resistance phenotype, *qnr* was discovered also in the absence of mutations on topoisomerase genes (Gunell et al., 2009). To this end there is no reliable way

for searching of all *qnr* determinants and it is possible that some *qnr* positive strains are not likely to be discovered (Cavaco and Aarestrup, 2009). The *qnr* determinants in *Salmonella* are present around the globe and as such pose a risk of therapy failure in patients requiring antibiotic treatment. In developed countries the *qnr* is often connected with foreign travel to countries where resistance to fluoroquinolones is more common or to imported foods (Gay et al., 2006; Hopkins et al., 2008; Taguchi et al., 2009, Sjölund-Karlsson et al., 2010).

For the monitoring on *qnr* in the communities in France, the extended-spectrum β-lactamases positive *Salmonella enterica* were included in the study. Only one out of 17 ESBL isolates were positive for the *qnrA* gene (Cattoir et al., 2007). In the UK, among cefotaxime resistant (MIC > 1μg/mL) *Salmonella enterica*, *qnrS* variants were found in serotypes: Stanley, Typhimuirum DT193, Virchow PT8 and Virginia (Hopkins et al., 2007). Plasmid dissemination contributed to spread of *qnr* genes and also its transferability could be due to integron like genetic structure (Hopkins et al., 2005). *Qnr* variants (*qnrA1*, *qnrB1*, *qnrB2*, *qnrB5* and *qnrS1*) were found in *Salmonella* , with reduced susceptibility to CIP, in Scotland. A total of 34 isolates out of 70 were *qnr* positive. Most of them were of human origin, 2 isolates was from ovine, 1 isolate from bovine and 1 from the environment. The most common serotype was Corvallis, Typhimurium, Stanley and Enteritidis. Those isolates were *qnrS1* positive. In *S.* Virchow and *S.* Stanley *qnrA1* was found. *S.* Colindale was the *qnrB1* positive, *S.* Agona and *S.* Haifa was *qnrB2* positive while *S.* Gaminara was *qnrB5* positive (Murray et al., 2008). The first occurrence on *qnr* positive *Salmonella* from Taiwan was provided by Wu et al., (2008). They discovered *qnrB2* and *qnrS1* in 4 isolates from the communities in Taiwan. For all isolates MIC to NAL was 32 μg/mL while to CIP it ranged from 0.19 to 0.38 μg/mL. In South Africa invasive *S.* Typhimuirum carrying the *qnrB2* gene was found, for the first time, from an immunocompromised patient. MIC to NAL was 32 μg/mL and to CIP it was 0.38 μg/mL (Govender et al., 2009). The *qnr* genes were found in 6 out of 284 clinical isolates of *Salmonella spp.* in Korea. The *qnr* variants identified were *qnrS1* in four isolates, *qnrB19* in two isolates while one isolate has *aac(6`)-lb-cr*. MIC to NAL ranged from 16 to >512 μg/mL, while to CIP it was 0.06 to 8 μg/mL. Among *qnr* positive isolates, the mutation in QRDR was found in *S.* Kentucky positive for *qnrS1*. The MIC to CIP was 8 μg/mL and amino acid substitution Thr57→Ser was found on *parC* gene (Jeong et al., 2011). The Thr57→Ser substitution is believed to be less involved in resistance to quinolones but as natural compensatory mutation it decreases resistance to fluoroquinolones (rev by Velhner and Stojanović, 2012). In another research from Korea 507 NAL resistant isolates were tested for plasmid mediated resistance determinants and it was shown that *aac(6`)-lb* is present in six isolates

from food animals. Four isolates (2 *S*. Typhimurium from pig and from cattle, one *S*. Derby from pork and one *S*. Essen from healthy cattle), was identified as *aac(6`)-lb-cr* positive. The obtained MIC to NAL was 512 μg/mL, MIC to CIP was 1 μg/mL and for enrofloxacin it was 1 μg/mL (Tamang et al., 2011). *Salmonella* Typhimuirum positive for *aac(6`)-lb-cr* was found in stool specimens from pediatric inpatients in Jiangxi Provincial Children's hospital in China. From 62 isolates, 23 were having *aac(6`)-lb-cr* gene and MIC to ciprofloxacin ranged from 0.5 to 4 μg/mL. In seven isolates bla_{CTX-M} gene was also found and all strains with MIC to CIP ≥ 2μg/mL had bla_{TEM} gene. High level of resistance to CIP was also attributed to point mutations on *gyrA* (codon 87). The authors found clonal relationship among 6 isolates of *S*. Typhimuirum carrying *aac(6`)-lb-cr* and bla_{CTX-M} genes (Yu et al., 2011). In Japan the *qnrS1* and *qnrS2* determinants were found in Salmonella isolated from patients who traveled overseas. MIC to NAL was 16 to 64 μg/mL, while to CIP it was from 0.25 to 2 μg/mL. There were no mutations detected on QRDR (Taguchi et al., 2009).

The research on *qnr* resistance determinants was conducted in the USA from the isolates collected in 2007 from humans and also from food producing animals. The *qnr* was found only in human isolates. According to the CLSI breakpoint, these isolates were susceptible to NAL and displayed reduced susceptibility to CIP. Animal isolates were NAL resistant suggesting mutation on QRDR. Two *S*. Typhimurium and 1 *S*. Corvalis were *qnrS1* positive. The *qnrB2* and *qnrB19* was found in *S*. Enteritidis and *S*. Beaudesert respectively. One isolate (*S*. Thompson) was *aac(6')-lb-cr* positive. The prevalence of *qnr* genes in the USA was the same as in previous years (Sjölund-Karlsson et al., 2010). International collaborative study was conducted in 13 European countries to determine *qnr* prevalence in *Salmonella enterica* and *E. coli* in respect to the following breakpoints (MIC to CIP in *Salmonella* ≥ 0.125 and ≥ 0.25 μg/mL), MIC to CIP ≥ 0.06 μg/mL in *E.coli*, and if MIC to NAL was 4-32 μg/mL. The screening method was done in total 66.1629 *Salmonella* sp. and 31.132 *E. coli* isolates. Qnr was identified in 485 *Salmonella* and 133 *E. coli* isolates. The *qnr* genes were found predominantly in *Salmonella* from humans, turkeys, fowls, pigs, sheep, reptiles, food and the environment. The *qnrS1* was the most frequent finding. It was found in *S*. Corvallis and *S*. Typhimurium from human specimens from The Netherlands and UK and *S*. Saintpaul from turkeys from Denmark, Poland and Germany. The *qnrB* was found from turkeys, humans, reptiles and fowls as a following variants: *qnrB2*, *qnrB4*, *qnrB6*, *qnrB7*, *qnrB12* and *qnrB19*. The *Salmonella* isolated from a turtle had *qnrB6* and *acc(6')-lb-cr* determinants. The *qnrD* was prevalently found in poultry isolates from Spain but also from fowls, turkeys and food from Italy and from two human specimens from The Netherlands. The *qnrA1* was evident in chic-

ken isolate of *S*. Paratyphi B variant Java from Belgium and The Netherlands and in *S*.Typhimurium found in turkeys from Germany. *E. coli* was *qnrS1* and *qnrB19* positive and was found in food, turkeys, cattle and pigs mostly from Poland (Veldman et al., 2011). During a survey on nontyphoidal *Salmonella* from chickens, conducted with the contribution of four European countries, Kehreneberg et al. (2006) found *qnrS* gene. The determinant was incorporated in the proximity of Tn*3* element. The insertion sequences IS*2*-like and IS26 were found. It is known that such sequences are responsible for the recombination of some gene clusters or genomic regions in *Enterobacteriaceae*. The evidence was made that Tn*3* was incorporated in a plasmid pINF5 in *S*. Infantis independently from *qnrS*. The first report on *qnr* positive *Salmonellae* in the Netherlands was provided by Veldman et al., 2008. A collection of isolates from humans, cattle, poultry, pigs and other, for the period from 1999 to 2006 was analysed. Only one poultry isolate was *qnrB2* positive, while human isolates had *qnrB2*, *qnrB5* and *qnrS1*. The first report on *qnr* determinants in *Salmonella* from Brazil was released by Ferrari et al., 2011. They found *qnrA1* in *S*. Enteritidis epidemic strain and *qnrB19* in *S*. Corvallis from poultry. The MIC to CIP was 0.062 and 0.5 μg/mL respectively.

The *qnr* determinants in *Salmonella* isolates from animals were studied in several countries. A strain collection consisting of *Salmonella* resistant to *β*-lactam antibiotics, collected from diarrheic calves in Egypt was investigated for resistance mechanisms. The $bla_{\text{TEM -1}}$ genes conferring resistance to β-lactames were found most frequently, but also other genes: *aadA1* or *aadA2* and *aadA5*, *dfrA1*, *dfrA15* conferring resistance to aminoglycosides and trimethoprim were detected. The *aadA* genes were found mostly in integrons class 1 and in one isolate in integron of class 2. Two *S*. Enteritidis isolates were *qnrS1* positive while one isolate of S. Typhimurium was *qnrB* positive. For the first time in Africa an *aac-(6')-lb-cr* gene was discovered in *S*. Enteritidis. This isolate was additionally positive to *qnrS* (Ahmed et al., 2009). *Salmonella* resistant to *β*-lactam antibiotics isolated from animals in Japan was found to carry: $bla_{\text{PSE-1}}$ or bla_{TEM}, *aadA2* or *aadA1*. These genes were differently distributed in integrons class 1 but also integrons class 2 was identified. In one isolate of *S*. Typhimurium from diseased beef and in one isolate of *S*. Thompson from healthy chicken the *qnrS1* was found, but resistance to *β*-lactam antibiotics was not detected. An isolate from diseased dairy cow was found to have *aadA2,* $bla_{\text{PSE-1}}$genes and *qnrS1*gene (Ahmed et al., 2009).

Monitoring of plasmid mediated resistance to quinolones is important although it is not as common as chromosomally directed resistance. The *qnr* determinants are more frequently reported from developing countries and in such cases it is usually connected with multiple drug resistance phenotypes.

However, it could be also found in *Salmonella* conferring intermediate resistance to fluoroquinolones. Polymerase chain reaction (PCR) detection of *qnr* genes is necessary and has to be implemented in Serbia as well.

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