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Review Article

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Clinical Importance and Epidemiology of Quinolone Resistance

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The quinolone class of antimicrobial agents is one of most widely used classes of antimicrobial agents in outpatient and inpatient treatment. However, quinolone resistance in gram-positive and gram-negative bacteria has emerged and increased globally. This resistance limits the usefulness of quinolones in clinical practice. The review summarizes mechanisms of quinolone resistance and its epidemiology and implications in the most common clinical settings, urinary tract infections, respiratory tract infections, intraabdominal infections, skin and skin structure infections, and sexually transmitted diseases.

Key Words: Quinolones; Drug resistance; Epidemiology; Mechanism; Clinical implications

Introduction

Quinolones to varying degrees inhibit the bacterial enzymes DNA gyrase and topoisomerase IV, which are responsible for introducing negative supercoils into DNA in the case of gyrase and for relieving topological stress arising from the translocation of transcription and replication complexes along DNA [1, 2]. Formation of drug-enzyme-DNA complexes blocks DNA replication [3]. Quinolones have been prescribed widely to treat respiratory tract infections, including tuberculosis, urinary tract infections (UTIs), intraabdominal infections, skin and skin structure infections, sexually transmitted diseases, and bone and joint infections. They have also been used for prophylaxis in neutropenic patients with cancers, in cirrhotic patients at risk for spontaneous bacterial peritonitis, and in urologic surgery [4, 5]. The national use of quinolones steadily increased from 1994 to 2000 in US intensive care units (ICUs), and this use was significantly associated with decreased overall susceptibility to ciprofloxacin in the same period [6]. The consumption of quinolones doubled during 2001-2012 in a Korean hospital with the increased ciprofloxacin resistance in clinical isolates of *Escherichia coli* in ICUs [7]. While newer class quinolones that expand the spectrum of activity to include gram-positive bacteria and even anaerobes have been developed, quinolone resistance has nonetheless increased in many bacterial species, and no new quinolones with activity against gram-negative bacteria greater than that of ciprofloxacin have yet become available. The increase in quinolone re-

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sistance is now threatening the clinical utility for treatment of diverse infections [2, 8]. This paper summarizes mechanisms of quinolone resistance and its epidemiology and clinical importance in major infectious diseases.

Mechanisms of quinolone resistance

Mechanisms of quinolone resistance are generally classified as three types: 1) chromosomal mutations altering the drug target enzymes to reduce drug binding, 2) chromosomal mutations that increase expression of native efflux pumps that can transport quinolones to the outside of the bacterial cell, and 3) plasmid-acquired resistance genes producing either protection of target enzymes, drug modification, or drug efflux [9].

Quinolone resistance mutations in the target enzymes generally occur first in the GyrA subunit of DNA gyrase in gram-negative bacteria or in the ParC subunit of topoisomerase IV in gram-positive bacteria [2]. These resistance mutations occur most often in a region referred to as the "quinolone-resistance-determining region (QRDR)", which encompasses amino acids 51 to 106 in GyrA and 23 to 176 in ParC, with positions 83 and 87 most common in GyrA and positions 80 and 84 most common in ParC [9-11]. These substitutions are thought to result in a reduced affinity of gyrase or topoisomerase IV for quinolones [12, 13]. In *Staphylococcus aureus* or *Streptococcus pneumoniae*, the primary target mutations occur most frequently in ParC [14, 15]. In both gram-negative and gram-positive bacteria, combinations of mutations in both GyrA and ParC generally result in progressively higher levels of resistance. Less often mutations in GyrB and ParE have also contributed to resistance in clinical isolates.

Bacteria have a number of energy-dependent efflux systems in the cell membrane and envelope that can facilitate extrusion of potentially toxic agents, and many of these efflux pumps have broad substrate profiles that can include quinolones [16]. AcrAB-TolC is the major pump contributing to quinolone resistance in *E. coli* [2]. Mutations in *acrR*, which represses *acrAB*, can increase pump expression [17]. In addition, mutations in *marR*, a repressor of *marA*, which activates *acrAB* and *tolC*, also causes an increase of efflux [18]. *marA* also decreases the expression of OmpF, outer membrane porin protein [19]. Consequently, *marR* mutations have the dual effect of decreasing influx and increasing efflux of quinolones. *acrAB* expression is also induced by exposure to salicylates and bile salts, and AcrAB confers relative resistance to bile salts, thereby facilitating the ability of *E. coli* to live the intestinal tract [20]. Efflux pumps that include quinolones among their substrates have also been associated with resistance in a number of other gram-negative bacteria, being most extensively studied in *Pseudomonas aeruginosa*. There are at least five known efflux pumps (MexAB-OprM, MexCDOpr-J, MexEF-OprN, MexXY-OprM, and MexVW-OprM) that have been shown to efflux quinolones in *P. aeruginosa* [21]. In *S. aureus*, quinolone resistance has been associated with increased expression of NorA, NorB, and NorC pumps with both *norA* and *norB* overexpression regularly found in resistant clinical isolates [2, 22, 23]. Efflux also contributes to quinolone resistance in *S. pneumoniae* and mycobacteria.

Plasmid-mediated quinolone resistance (PMQR) was discovered in 1998 in a clinical isolate of *Klebsiella pneumoniae* that could transfer low-level quinolone resistance to gram-negative bacteria [24]. The responsible gene for PMQR was named *qnr* (later designated *qnrA*), and Qnr protein was shown to bind and protect DNA gyrase and topoisomerase IV from inhibition by ciprofloxacin [2]. Qnr itself provides only low-level resistance to quinolones, but its presence can facilitate the selection of additional resistance mutations [2]. It was soon discovered in a growing number of organisms and is broadly distributed geographically, including other *K. pneumoniae* strains in the United States [25, 26], *E. coli* isolates in Shanghai [27], and *Salmonella enterica* strains in Hong Kong [28]. *qnrA* was subsequently followed by discovery of plasmid-mediated *qnrS* [29], *qnrB* [30], *qnrC* [31], and *qnrD* [32]. The *qnrVC* gene from *Vibrio cholerae* can also be located on a plasmid [33-35] or in transmissible form as part of an integrating conjugative element [36]. Recently, other PMQR mechanisms were identified. One is *aac (6')-Ib-cr*, which is a variant of *aac (6')-Ib*, which encodes an aminoglycoside acetyltransferase [37]. AAC (6')-Ib-cr confers low-level ciprofloxacin resistance by acetylation of ciprofloxacin at the amino nitrogen on its piperazinyl substituent. *aac (6')-Ib-cr* has also been associated with other PMQR genes including diverse *qnr* genes and beta-lactamase genes [38]. The other PMQR mechanism is plasmid-mediated quinolone efflux. Two plasmid-mediated quinolone transporters have now been found: OqxAB [39] and QepA [40].

Urinary tract infections

E. coli, other Enterobacteriaceae, and *Enterococcus* spp. are the primary etiology of uncomplicated UTIs, with *E. coli* accounting more than 75% of isolates [41]. Quinolones have been widely used for the treatment of UTI because of their *in vitro*

activity and high efficacy, especially in acute pyelonephritis and in catheter-associated UTIs [42, 43]. However, the increased use of quinolones has been associated with increased rates of quinolone-resistance in clinical uropathogens.

The overall resistant rate of ciprofloxacin for outpatient *E. coli* urinary isolates in the US and Canada during 2003-2004 (North American Urinary Tract Infection Collaborative Alliance, NAUTICA) was 5.4% [44]. However, the ciprofloxacin resistance rate exceeded 20% in some areas. The ARESC (Antimicrobial Resistance Epidemiological Survey on Cystitis) study, which was performed in nine European countries including Russia and in Brazil during 2003-2006, showed that the ciprofloxacin resistance for *E. coli* isolates in the healthy women having uncomplicated lower UTIs was 8.3% [41]. Higher resistance rates, however, were found in several countries, including Brazil (10.8%), Spain (10.7%), Italy (12.5%), and Russia (13.6%). A recent surveillance study for gram-negative pathogens causing UTIs in Asia-Pacific regions, the SMART (the Study for Monitoring Antimicrobial Resistance Trends) study, showed 48.6% resistance to ciprofloxacin with wide range among different countries, from 10.0% in New Zealand to as high as 76.2% in Vietnam and 72.0% in China [45]. A nationwide study performed in 2006-2007 in Korea also showed 28.4% ciprofloxacin resistance for *E. coli* isolates causing community-onset UTIs with dissemination of epidemic and virulent ciprofloxacin-resistant *E. coli* clones such as sequence type 131 (ST131) and ST393 [46]. In a recent prospective Korean nationwide surveillance during 2010-2012, the ciprofloxacin resistance in *E. coli* isolates from women having community-acquired acute pyelonephritis was 20.0% [47]. Another multicenter study in 2012 also showed similar (22.5%) ciprofloxacin resistance in *E. coli* isolates from Korean women having community-associated acute pyelonephritis [48].

The known risk factors for quinolone resistance in uropathogenic *E. coli* isolated from community-onset acute pyelonephritis are prior exposure to quinolones, previous hospitalization, recurrent UTIs, previous invasive procedures, the presence of complicated UTIs, chronic diseases including neurologic diseases, age over 50 years, and presence of a urinary catheter in the past 6 months [48-55]. It is not surprising that most of these studies showed that prior exposure to quinolones was a significant risk factor for quinolone resistance in uropathogenic *E. coli*, because quinolone use was known to correlate with resistance of *E. coli* isolates to quinolones [56-60]. Another concern caused by quinolone resistance is its high association with extended spectrum beta-lactamase (ESBL) production in Enterobacteriaceae [61]. The mechanism of this association is not fully known. The interplay between prior heavy antibiotic use and conditions favoring patient-to-patient transfer of multidrug-resistant organisms or the occurrence of transferable plasmids carrying genes conferring resistance to quinolones and other antimicrobials could be contributing factors [2, 61]. The choice of appropriate antibiotics can be very limited in quinolone-resistant, ESBL-producing uropathogens because of their mutlidrug-resistant nature.

The clinical impact of increasing quinolone resistance in UTIs has contributed in part to the recent guideline in 2010 by the Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases (ESCMID) recommending non-quinolone antibiotics such as ceftriaxone or aminoglycoside for initial treatment of acute pyelonephritis in locations where the resistance rate of community uropathogens exceeds 10% [42]. Quinolones are not recommended as a first-line option for empiric treatment of serious complicated UTIs in some countries in the Asia-Pacific region with high rates of quinolone resistance (>20%) [62]. However, data are insufficient to make a recommendation about what quinolone resistance level requires an alternative agent in conjunction with or to replace a fluoroquinolone for treatment of pyelonephritis [42]. Whether the quinolone resistance of uropathogens affects clinical outcomes of patients with UTIs is controversial, since high drug concentrations in urine can be achieved in patients with normal renal function. There are few studies dealing with these issues. Discordant treatment for patients with community-acquired bacteremic acute pyelonephritis, most of which were caused by ciprofloxacin-resistant *E. coli*, was associated with poorer clinical outcomes in one Korean study [63]. In another study in Korea where the prevalence of ciprofloxacin resistance exceeds 10%, use of ciprofloxacin for initial empirical therapy of community-onset uncomplicated acute pyelonephritis caused by *E. coli* had no serious adverse outcomes, if its use was modified appropriately on the basis of susceptibility data, even for women infected with ciprofloxacin-resistant *E. coli* [64]. However, this study had an insufficient statistical power to detect a 10% difference due to a limited number of enrolled cases. Clinicians usually follow the breakpoints set for blood stream infections for the susceptibilities of urinary isolates of Enterobacteriaceae for commonly used quinolones such as ciprofloxacin and levofloxacin because there are no UTI-specific breakpoints in the recommendations of Clinical Laboratory Standard Institute (CLSI) [65]. It is noteworthy that correlations of resistance and outcome appeared better for UTIs complicated by bacte-

remia. Further studies are warranted to determine if UTI-specific breakpoints may provide more accurate predictions of clinical outcomes in UTI without bacteremia.

Respiratory tract infections

S. pneumoniae is a major cause of community-acquired pneumonia, and guidelines for empiric antibiotic choices always list anti-pneumococcal antibiotics, including respiratory quinolones [66, 67]. The emergence of pneumococcal resistance to the beta-lactam and macrolide antimicrobials has raised concerns regarding the use of these agents for the treatment of pneumococcal infections. Therefore, respiratory quinolones such as levofloxacin, moxifloxacin, and gemifloxacin are selectively recommended for the treatment of patients having community-acquired pneumonia. As the use of quinolones increased, fluoroquinolone-resistant *S. pneumoniae* has emerged in many countries and increased in some hot spots such as Canada, Spain, and Hong Kong [68].

The resistance rates of *S. pneumoniae* for respiratory quinolones in North America remain low (<2%) [69, 70]. In European countries, pneumococcal resistance to quinolones was reported to be 5.2% in 2012 [71]. However, it was very low (<0.7%) in two German multicenter studies (MOXIAKTIV Study and German CAPNETZ surveillance study) [72, 73]. The resistance rates to quinolones in the Asian Network for Surveillance of Resistant Pathogens (ANSORP) showed resistance rates of 1.7% and 0.4% for levofloxacin and moxifloxacin, respectively, with highest rates of levofloxacin resistance in isolates from Taiwan (6.5%) and Korea (4.6%) [74].

The known risk factors for infection or colonization by levofloxacin-resistant *S. pneumoniae* are previous exposure to quinolones, healthcare-associated infection, residence in a nursing home, presence of chronic obstructive pulmonary disease, and presence of cerebrovascular disease [75-77]. Fluoroquinolone resistance was not observed in a German study in spite of high usage of fluoroquinolones for the treatment of patients having community-acquired pneumonia [73]. The authors speculated that the low resistance may be related to the greater usage of levofloxacin or moxifloxacin relative to other quinolones with lower potency for the treatment of community-acquired pneumonia.

The clinical implications of quinolone resistance in *S. pneumoniae* have been little studied. The influence of the resistance on the overall 30-day mortality was conflicting [77, 78], but the numbers of the cases of levofloxacin-resistant *S. pneumoniae* have been relatively small, limiting the power of these studies to correlate resistance and clinical outcome. Further investigations that include more cases with resistant *S. pneumoniae* will be needed to assess the clinical implications in community-acquired pneumonia. A fatal levofloxacin failure case has been reported in treatment of a bacteremic patient infected with levofloxacin-resistant *S. pneumoniae* [79]. It is likely that in the presence of bacteremia complicating pneumococcal pneumonia outcomes for resistant *S. pneumoniae* may be poor.

Haemophilus influenzae and *Moraxella catarrhalis*, which are also important respiratory pathogens in community-acquired pneumonia, have largely remained highly susceptible to quinolones [72, 80]. For respiratory pathogens isolated from healthcare-associated pneumonia, such as Enterobacteriaceae, *P. aeruginosa*, and *Acinetobacter baumannii*, the quinolone resistance rates have been higher, but with regional differences [81-85]. A prospective surveillance study conducted by the ANSORP from 2008-2009 also showed a high ciprofloxacin resistance profile of *K. pneumoniae* (31.2%), *P. aeruginosa* (30.1%), and *Acinetobacter* spp. (80.7%) in Asian countries, including Korea [81]. Quinolone-resistant isolates were frequently multidrug-resistant. Local resistance patterns should be considered when quinolones are prescribed for the treatment of healthcare-associated pneumonia.

Intraabdominal infections

Intraabdominal infections are usually caused by mixed aerobic and anaerobic microorganisms, and the major pathogens in community-acquired intraabdominal infections are coliforms (Enterobacteriaceae, especially *E. coli*) and *Bacteroides fragilis* [86]. Among quinolones, moxifloxacin as a single agent therapy or a combination of metronidazole with ciprofloxacin or levofloxacin has been recommended for the treatment of mild to moderate community-acquired intraabdominal infections. Combination therapy with metronidazole and quinolones is an option for the patients with high-severity community-acquired intraabdominal infections [86].

In the study for monitoring antimicrobial resistance trends, ciprofloxacin susceptibility of *E. coli* isolates from the patients having intraabdominal infections at 37 hospital centers in North America has decreased from 84.4% to 72.2% between 2005 and 2010 [87]. For other major pathogens such as *K. pneumoniae*, *P. aeruginosa*, *Enterobacter cloacae*, *Klebsiella oxytoca*, and *Proteus mirabilis*, the susceptibilities for quino-

lones remained stable. In Europe, ciprofloxacin resistance of *E. coli* isolates from community-associated or hospital-associated intraabdominal infections in 2008 was 17.8% and 29.5%, respectively [88]. The quinolone resistance of *E. coli* isolates from intraabdominal infections in Asia has been more serious with >60% ciprofloxacin resistance in *E. coli* in China [89-91]. In a recent study, quinolone resistance of gram-negative bacilli, most of which were *E. coli* and *K. pneumoniae*, in bacteremic intraabdominal infections was 22.9% in Korea [92]. The quinolone resistance in *E. coli* strains in fecal flora was related to the recent quinolone use [93]. In a Spanish study, a strong linkage between quinolone resistance in *E. coli* in human fecal flora and quinolone use in food animals, especially poultry, was also suggested [94]. The prevalence of quinolone-resistant *E. coli* in the feces of healthy persons in the community, including children who had never received quinolones, was high (24% in adults and 26% in children). Therefore, the increase of quinolone resistance in *E. coli* in intraabdominal infections is likely the result of increasing quinolone use.

A surveillance study on antimicrobial susceptibility in clinical isolates of *Bacteroides* spp. from 13 European countries in 2008-2009 showed that the overall resistance rate to moxifloxacin also increased from 9% to 13.6% [95]. While the current guideline recommends a quinolone as one choice for treatment of community-acquired intraabdominal infections, quinolones should not be used unless hospital surveys indicate >90% susceptibility of *E. coli* to quinolones [86].

Salmonella spp., including serovar Typhi and Paratyphi, with reduced susceptibility to the fluoroquinolones have increased in humans and animals, especially in Europe, Southeast Asia, and the Indian subcontinent [96]. While the ciprofloxacin non-susceptible *S.* Typhi or *S.* Paratyphi which show a minimal inhibitory concentration (MIC) >1 μg/mL were not common, strains with reduced susceptibility to ciprofloxacin or resistance to nalidixic acid represented > 90% of strains in India and Vietnam, and included a high prevalence of multidrug resistance [97]. The response to fluoroquinolones is known to be impaired in infections with *S. typhi* isolates that have reduced susceptibility to ciprofloxacin, with longer fever clearance times and more frequent treatment failures.

Quinolone resistance in *Shigella* has also become serious globally, especially in Asia and Africa. In a systematic review, resistance rates to nalidixic acid and ciprofloxacin in the Asia-Africa region were 33.6% and 5.0%, respectively, values 10.5 and 16.7 times those of the Europe-America region [98]. Moreover, resistance to nalidixic acid and ciprofloxacin in Asia–Africa progressively increased each year, reaching 64.5% and 29.1%, respectively, in 2007–2009, while isolates in Europe-America remained at low levels of resistance (<5.0% and <1.0%, respectively). There are few reports of clinical failures in association with reduced susceptibility to quinolones or resistance to nalidixic acid [99, 100], but those strains may be associated with a worse clinical outcome and failure of bacterial eradication when treated with ciprofloxacin [101].

Resistance to ciprofloxacin or nalidixic acid in *Campylobacter* spp. is common in the US and in Europe, with a higher prevalence in *Campylobacter coli* than *Campylobacter jejuni* [102]. These high levels of resistance have been related to veterinary use of quinolones with increasing quinolone resistance in both animals and humans [96]. The rate of ciprofloxacin-resistant *Campylobacter* isolates from humans with gastroenteritis was 24% in a nationwide surveillance in Korea in 2007-2009 [103]. Most cases of *Campylobacter* enteritis do not require antimicrobial treatment, because it is usually a mild and self-limiting illness. However, *Campylobacter* isolates that are resistant to ciprofloxacin have also been associated with bacteriologic or clinical treatment failure [104, 105].

Skin and skin structure infections

The most common pathogens in skin and skin structure infections are *S. aureus* and *Streptococcus pyogenes*. They are also major pathogens in complicated skin and skin structure infections with polymicrobial etiology that also include gram-negative organisms and anaerobes. The quinolones have antibacterial activity for many of these pathogens, excellent oral bioavailability, and favorable penetration into soft tissues [106].

S. pyogenes has been universally susceptible to beta-lactams, which are the drugs of choice for treatment, and quinolones are generally not indicated for treating *S. pyogenes* in-fections. While the incidence of quinolone resistance in *S. pyogenes* is still low globally [107], some surveillance studies have revealed an increase of the prevalence of *S. pyogenes* with reduced susceptibility to quinolones [108, 109].

For staphylococci, the early investigations with the new fluoroquinolones, particularly ciprofloxacin, demonstrated *in vitro* activity against both methicillin-susceptible and methicillin-resistant staphylococci [110, 111]. However, quinolone resistance developed rapidly in the early days of quinolone therapy for methicillin-resistant *S. aureus* (MRSA) usually in the healthcare setting. While quinolone resistance in methicillin-susceptible *S. aureus* (MSSA) is substantially less com-

mon, resistance in MRSA is common worldwide, including Korea [112, 113]. A recent international study showed a similar difference in levofloxacin resistance profiles between MSSA and MRSA isolates from complicated skin and skin structure infections: 11.1% versus 70.3%, respectively [114]. Community-associated MRSA (CA-MRSA) has emerged in many countries and showed susceptibility to a wide variety of non-beta-lactam antimicrobials, including quinolones [115]. CA-MRSA was the most common identifiable cause of skin and soft tissue infections among patients treated in US emergency rooms, and most clones were of the USA300 pulsed-field type containing Panton-Valentine leukocidin [116]. In a recent study, however, only 57.4% of USA300 isolates from complicated skin and skin structure infections in Europe and America were susceptible to gatifloxacin, indicating a marked change quinolone susceptibility of CA-MRSA [117].

Quinolones alone or in combination with other antibiotics can be one of option for treatment of mild to moderate diabetic foot infections, which are frequently mixed infections [118]. They can be especially useful to treat combined osteomyelitis due to their ability to penetrate bone tissue [119]. Quinolones with other antibiotics such as anti-MRSA and/or anti-anaeroblic agents also can be used for empiric treatment of complicated polymicrobial skin and skin structure infection, such as polymicrobial necrotizing fasciitis [120]. However, increasing resistance, especially in MRSA, frequently limits the wide use of quinolones in skin and skin structure infections. Thus, quinolones should be used with caution in skin and skin structure infections.

Sexually transmitted diseases

Fluoroquinolones were once highly effective antimicrobials in treating gonococcal infections, and ciprofloxacin was recommended by the US Centers for Disease Control and Prevention (CDC) treatment guideline in 1993 [121]. However, ciprofloxacin resistance emerged in *Neisseria gonorrheae* in Hawaii and the West Coast in the late 1990s and by 2004 had also emerged in men who have sex with men. By 2006, 13.8% of *N. gonorrheae* isolates exhibited resistance to ciprofloxacin with its presence in all US regions and the heterosexual population. The prevalence of ciprofloxacin-resistant *N. gonorrheae* isolates from male patients also increased from 26% in 2000 to 83% in 2006 in Korea [122]. Treatment failure was very frequent in treating with ciprofloxacin for quinolone-resistant *N. gonorrheae* infection [123]. The dissemination of the quinolone resistance in *N. gonorrheae* was facilitated by the failure of treatment to eradicate the organism, resulting in an increased likelihood for person-to-person transmission, locally, nationally, and internationally [96]. CDC stopped recommending fluoroquinolones as empiric treatment for gonococcal infections in 2007 [124].

Conclusion

The quinolones are an important and widely used class of antimicrobial agents in clinical medicine. Resistance has, however, become widespread in a number of human pathogens driven in part by use of quinolones in humans. Physicians should be aware of risk factors associated with quinolone resistance, the most important of which is prior quinolone exposure. Although there has been a controversy about the clinical implications of quinolone resistance in some clinical situations, such as UTIs, resistance has frequently limited the use of these useful antibiotics, and is particularly likely to adversely affect outcomes in bacteremic patients or patients with infections at sites of poor drug delivery. Ongoing surveillance of local and national resistance trends will be important, and careful and select use of quinolones will be warranted.

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