Review Article

http://dx.doi.org/10.3947/ic.2014.46.4.226
Infect Chemother 2014;46(4):226-238
ISSN 2093-2340 (Print) · ISSN 2092-6448 (Online)

ic Infection & Chemotherapy

Clinical Importance and Epidemiology of Quinolone Resistance

Eu Suk Kim[1,2], and David C. Hooper[1]

[1]Division of Infectious Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [2]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

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-

Received: December 4, 2014
Corresponding Author : David C Hooper
Division of Infectious Diseases, Massachusetts General Hospital,
55 Fruit Street, Boston, MA 02114-2696, USA.
Tel: +1-617-726-3812, Fax: +1-617-726-7416
E-mail: dhooper@mgh.harvard.edu

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.

References

1. Hawkey PM. Mechanisms of quinolone action and microbial response. J Antimicrob Chemother 2003;51 (Suppl 1):29-35.
2. Jacoby GA. Mechanisms of resistance to quinolones. Clin Infect Dis 2005;41 (Suppl 2):S120-6.
3. Hiasa H, Shea ME. DNA gyrase-mediated wrapping of the DNA strand is required for the replication fork arrest by the DNA gyrase-quinolone-DNA ternary complex. J Biol Chem 2000;275:34780-6.
4. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR, Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52:427-31.
5. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA; American Society of Health-System Pharmacists; Infectious Disease Society of

America; Surgical Infection Society; Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013;70:195-283.
6. Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. JAMA 2003;289:885-8.
7. Jun KI, Koo HL, Kim MK, Kang CK, Kim MJ, Chun SH, Song JS, Kim HS, Kim NJ, Kim EC, Oh MD. Trends in antibiotic use in a single university hospital. Korean J Nosocomial Infect Control 2013;18:44-50.
8. Thauvin-Eliopoulos C, Eliopoulos GM. Activity *in vitro* of the quinolones. In: Hooper DC, Rubinstein E, eds. Quinolone Antimicrobial Agents. 3rd ed. Washington, DC: American Society for Microbiology Press; 2003;91-111.
9. Hooper DC. Mechanism of quinolone resistance. In: Hooper DC, Rubinstein E, eds. Quinolone Antimicrobial Agents. 3rd ed. Washington, DC: American Society for Microbiology Press; 2003;41-67.
10. Yoshida H, Bogaki M, Nakamura M, Nakamura S. Quinolone resistance-determining region in the DNA gyrase *gyrA* gene of *Escherichia coli*. Antimicrob Agents Chemother 1990;34:1271-2.
11. Friedman SM, Lu T, Drlica K. Mutation in the DNA gyrase A gene of *Escherichia coli* that expands the quinolone resistance-determining region. Antimicrob Agents Chemother 2001;45:2378-80.
12. Barnard FM, Maxwell A. Interaction between DNA gyrase and quinolones: effects of alanine mutations at GyrA subunit residues Ser(83) and Asp(87). Antimicrob Agents Chemother 2001;45:1994-2000.
13. Willmott CJ, Maxwell A. A single point mutation in the DNA gyrase A protein greatly reduces binding of fluoroquinolones to the gyrase-DNA complex. Antimicrob Agents Chemother 1993;37:126-7.
14. Ng EY, Trucksis M, Hooper DC. Quinolone resistance mutations in topoisomerase IV: relationship to the *flqA* locus and genetic evidence that topoisomerase IV is the primary target and DNA gyrase is the secondary target of fluoroquinolones in *Staphylococcus aureus*. Antimicrob Agents Chemother 1996;40:1881-8.
15. Eliopoulos GM. Quinolone resistance mechanisms in pneumococci. Clin Infect Dis 2004; 38 (Suppl 4):S350-6.
16. Poole K. Efflux-mediated antimicrobial resistance. J Antimicrob Chemother 2005;56:20-51.
17. Wang H, Dzink-Fox JL, Chen M, Levy SB. Genetic characterization of highly fluoroquinolone-resistant clinical *Escherichia coli* strains from China: role of *acrR* mutations. Antimicrob Agents Chemother 2001;45:1515-21.
18. Alekshun MN, Levy SB. Regulation of chromosomally mediated multiple antibiotic resistance: the *mar* regulon. Antimicrob Agents Chemother 1997;41:2067-75.
19. Cohen SP, McMurry LM, Hooper DC, Wolfson JS, Levy SB. Cross-resistance to fluoroquinolones in multiple-antibiotic-resistant (Mar) *Escherichia coli* selected by tetracycline or chloramphenicol: decreased drug accumulation associated with membrane changes in addition to OmpF reduction. Antimicrob Agents Chemother 1989;33:1318-25.
20. Thanassi DG, Cheng LW, Nikaido H. Active efflux of bile salts by *Escherichia coli*. J Bacteriol 1997;179:2512-8.
21. Zhanel GG, Hoban DJ, Schurek K, Karlowsky JA. Role of efflux mechanisms on fluoroquinolone resistance in *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*. Int J Antimicrob Agents 2004;24:529-35.
22. Kosmidis C, Schindler BD, Jacinto PL, Patel D, Bains K, Seo SM, Kaatz GW. Expression of multidrug resistance efflux pump genes in clinical and environmental isolates of *Staphylococcus aureus*. Int J Antimicrob Agents 2012;40:204-9.
23. Kwak YG, Truong-Bolduc QC, Bin Kim H, Song KH, Kim ES, Hooper DC. Association of *norB* overexpression and fluoroquinolone resistance in clinical isolates of *Staphylococcus aureus* from Korea. J Antimicrob Chemother 2013;68:2766-72.
24. Martínez-Martínez L, Pascual A, Jacoby GA. Quinolone resistance from a transferable plasmid. Lancet 1998;351:797-9.
25. Rodríguez-Martínez JM, Pascual A, García I, Martínez-Martínez L. Detection of the plasmid-mediated quinolone resistance determinant *qnr* among clinical isolates of *Klebsiella pneumoniae* producing AmpC-type beta-lactamase. J Antimicrob Chemother 2003;52:703-6.
26. Wang M, Sahm DF, Jacoby GA, Hooper DC. Emerging plasmid-mediated quinolone resistance associated with the *qnr* gene in *Klebsiella pneumoniae* clinical isolates in the United States. Antimicrob Agents Chemother 2004;48:1295-9.
27. Wang M, Tran JH, Jacoby GA, Zhang Y, Wang F, Hooper DC. Plasmid-mediated quinolone resistance in clinical isolates of *Escherichia coli* from Shanghai, China. Antimicrob Agents Chemother 2003;47:2242-8.
28. Cheung TK, Chu YW, Chu MY, Ma CH, Yung RW, Kam KM. Plasmid-mediated resistance to ciprofloxacin and cefotaxime in clinical isolates of *Salmonella enterica* serotype Enteritidis in Hong Kong. J Antimicrob Chemother 2005;56:586-9.

29. Hata M, Suzuki M, Matsumoto M, Takahashi M, Sato K, Ibe S, Sakae K. Cloning of a novel gene for quinolone resistance from a transferable plasmid in *Shigella flexneri* 2b. Antimicrob Agents Chemother 2005;49:801-3.
30. Jacoby GA, Walsh KE, Mills DM, Walker VJ, Oh H, Robicsek A, Hooper DC. *qnrB*, another plasmid-mediated gene for quinolone resistance. Antimicrob Agents Chemother 2006;50:1178-82.
31. Wang M, Guo Q, Xu X, Wang X, Ye X, Wu S, Hooper DC, Wang M. New plasmid-mediated quinolone resistance gene, *qnrC*, found in a clinical isolate of *Proteus mirabilis*. Antimicrob Agents Chemother 2009;53:1892-7.
32. Cavaco LM, Hasman H, Xia S, Aarestrup FM. *qnrD*, a novel gene conferring transferable quinolone resistance in *Salmonella enterica* serovar Kentucky and Bovismorbificans strains of human origin. Antimicrob Agents Chemother 2009;53:603-8.
33. Xia R, Guo X, Zhang Y, Xu H. *qnrVC*-like gene located in a novel complex class 1 integron harboring the ISCR1 element in an *Aeromonas punctata* strain from an aquatic environment in Shandong Province, China. Antimicrob Agents Chemother 2010;54:3471-4.
34. Singh R, Rajpara N, Tak J, Patel A, Mohanty P, Vinothkumar K, Chowdhury G, Ramamurthy T, Ghosh A, Bhardwaj AK. Clinical isolates of *Vibrio fluvialis* from Kolkata, India, obtained during 2006: plasmids, the *qnr* gene and a mutation in *gyrase A* as mechanisms of multidrug resistance. J Med Microbiol 2012;61:369-74.
35. Fonseca EL, Vicente AC. Epidemiology of *qnrVC* alleles and emergence out of the *Vibrionaceae* family. J Med Microbiol 2013;62:1628-30.
36. Kim HB, Wang M, Ahmed S, Park CH, LaRocque RC, Faruque AS, Salam MA, Khan WA, Qadri F, Calderwood SB, Jacoby GA, Hooper DC. Transferable quinolone resistance in *Vibrio cholerae*. Antimicrob Agents Chemother 2010;54:799-803.
37. Robicsek A, Strahilevitz J, Jacoby GA, Macielag M, Abbanat D, Park CH, Bush K, Hooper DC. Fluoroquinolone-modifying enzyme: a new adaptation of a common aminoglycoside acetyltransferase. Nat Med 2006;12:83-8.
38. Strahilevitz J, Jacoby GA, Hooper DC, Robicsek A. Plasmid-mediated quinolone resistance: a multifaceted threat. Clin Microbiol Rev 2009;22:664-89.
39. Hansen LH, Johannesen E, Burmølle M, Sørensen AH, Sørensen SJ. Plasmid-encoded multidrug efflux pump conferring resistance to olaquindox in *Escherichia coli*. Antimicrob Agents Chemother 2004;48:3332-7.
40. Yamane K, Wachino J, Suzuki S, Kimura K, Shibata N, Kato H, Shibayama K, Konda T, Arakawa Y. New plasmid-mediated fluoroquinolone efflux pump, QepA, found in an *Escherichia coli* clinical isolate. Antimicrob Agents Chemother 2007;51:3354-60.
41. Schito GC, Naber KG, Botto H, Palou J, Mazzei T, Gualco L, Marchese A. The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. Int J Antimicrob Agents 2009;34:407-13.
42. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-20.
43. Hooton TM, Bradley SF, Cardenas DD, Colgan R, Geerlings SE, Rice JC, Saint S, Schaeffer AJ, Tambayh PA, Tenke P, Nicolle LE; Infectious Diseases Society of America. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis 2010;50:625-63.
44. Zhanel GG, Hisanaga TL, Laing NM, DeCorby MR, Nichol KA, Weshnoweski B, Johnson J, Noreddin A, Low DE, Karlowsky JA; NAUTICA Group, Hoban DJ. Antibiotic resistance in *Escherichia coli* outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). Int J Antimicrob Agents 2006;27:468-75.
45. Lu PL, Liu YC, Toh HS, Lee YL, Liu YM, Ho CM, Huang CC, Liu CE, Ko WC, Wang JH, Tang HJ, Yu KW, Chen YS, Chuang YC, Xu Y, Ni Y, Chen YH, Hsueh PR. Epidemiology and antimicrobial susceptibility profiles of Gram-negative bacteria causing urinary tract infections in the Asia-Pacific region: 2009-2010 results from the Study for Monitoring Antimicrobial Resistance Trends (SMART). Int J Antimicrob Agents 2012;40 (Suppl):S37-43.
46. Lee MY, Choi HJ, Choi JY, Song M, Song Y, Kim SW, Chang HH, Jung SI, Kim YS, Ki HK, Son JS, Kwon KT, Heo ST, Yeom JS, Shin SY, Chung DR, Peck KR, Song JH, Ko KS. Dissemination of ST131 and ST393 community-onset, ciprofloxacin-resistant *Escherichia coli* clones causing urinary tract infections in Korea. J Infect 2010;60:146-53.

47. Kim Y, Wie SH, Chang UI, Kim J, Ki M, Cho YK, Lim SK, Lee JS, Kwon KT, Lee H, Cheong HJ, Park DW, Ryu SY, Chung MH, Pai H. Comparison of the clinical characteristics of diabetic and non-diabetic women with community-acquired acute pyelonephritis: a multicenter study. J Infect 2014;69:244-51.
48. Park KH, Oh WS, Kim ES, Park SW, Hur JA, Kim YK, Moon C, Lee JH, Lee CS, Kim BN. Factors associated with ciprofloxacin- and cefotaxime-resistant *Escherichia coli* in women with acute pyelonephritis in the emergency department. Int J Infect Dis 2014;23:8-13.
49. Chaniotaki S, Giakouppi P, Tzouvelekis LS, Panagiotakos D, Kozanitou M, Petrikkos G, Avlami A, Vatopoulos AC; WHONET Study Group. Quinolone resistance among *Escherichia coli* strains from community-acquired urinary tract infections in Greece. Clin Microbiol Infect 2004;10:75-8.
50. Killgore KM, March KL, Guglielmo BJ. Risk factors for community-acquired ciprofloxacin-resistant *Escherichia coli* urinary tract infection. Ann Pharmacother 2004;38:1148-52.
51. Arslan H, Azap OK, Ergönül O, Timurkaynak F; Urinary Tract Infection Study Group. Risk factors for ciprofloxacin resistance among *Escherichia coli* strains isolated from community-acquired urinary tract infections in Turkey. J Antimicrob Chemother 2005;56:914-8.
52. Johnson L, Sabel A, Burman WJ, Everhart RM, Rome M, MacKenzie TD, Rozwadowski J, Mehler PS, Price CS. Emergence of fluoroquinolone resistance in outpatient urinary *Escherichia coli* isolates. Am J Med 2008;121:876-84.
53. van der Starre WE, van Nieuwkoop C, Paltansing S, van't Wout JW, Groeneveld GH, Becker MJ, Koster T, Wattel-Louis GH, Delfos NM, Ablij HC, Leyten EM, Blom JW, van Dissel JT. Risk factors for fluoroquinolone-resistant *Escherichia coli* in adults with community-onset febrile urinary tract infection. J Antimicrob Chemother 2011;66:650-6.
54. Vellinga A, Tansey S, Hanahoe B, Bennett K, Murphy AW, Cormican M. Trimethoprim and ciprofloxacin resistance and prescribing in urinary tract infection associated with *Escherichia coli*: a multilevel model. J Antimicrob Chemother 2012;67:2523-30.
55. Colodner R, Kometiani I, Chazan B, Raz R. Risk factors for community-acquired urinary tract infection due to quinolone-resistant *E. coli*. Infection 2008;36:41-5.
56. Cizman M, Orazem A, Krizan-Hergouth V, Kolman J. Correlation between increased consumption of fluoroquinolones in outpatients and resistance of *Escherichia coli* from urinary tract infections. J Antimicrob Chemother 2001;47:502.
57. Zervos MJ, Hershberger E, Nicolau DP, Ritchie DJ, Blackner LK, Coyle EA, Donnelly AJ, Eckel SF, Eng RH, Hiltz A, Kuyumjian AG, Krebs W, McDaniel A, Hogan P, Lubowski TJ. Relationship between fluoroquinolone use and changes in susceptibility to fluoroquinolones of selected pathogens in 10 United States teaching hospitals, 1991-2000. Clin Infect Dis 2003;37:1643-8.
58. MacDougall C, Powell JP, Johnson CK, Edmond MB, Polk RE. Hospital and community fluoroquinolone use and resistance in *Staphylococcus aureus* and *Escherichia coli* in 17 US hospitals. Clin Infect Dis 2005;41:435-40.
59. Mahamat A, Daurès JP, Sotto A. Evaluation of the relation between consumption of fluoroquinolones and emergence of resistance among *Escherichia coli*: contribution of observational and quasi-experimental studies. Med Mal Infect 2005;35:543-8.
60. Gallini A, Degris E, Desplas M, Bourrel R, Archambaud M, Montastruc JL, Lapeyre-Mestre M, Sommet A. Influence of fluoroquinolone consumption in inpatients and outpatients on ciprofloxacin-resistant *Escherichia coli* in a university hospital. J Antimicrob Chemother 2010;65:2650-7.
61. Paterson DL, Mulazimoglu L, Casellas JM, Ko WC, Goossens H, Von GA, Mohapatra S, Trenholme GM, Klugman KP, McCormack JG, Yu VL. Epidemiology of ciprofloxacin resistance and its relationship to extended-spectrum beta-lactamase production in *Klebsiella pneumoniae* isolates causing bacteremia. Clin Infect Dis 2000;30:473-8.
62. Hsueh PR, Hoban DJ, Carmeli Y, Chen SY, Desikan S, Alejandria M, Ko WC, Binh TQ. Consensus review of the epidemiology and appropriate antimicrobial therapy of complicated urinary tract infections in Asia-Pacific region. J Infect 2011;63:114-23.
63. Lee SS, Kim Y, Chung DR. Impact of discordant empirical therapy on outcome of community-acquired bacteremic acute pyelonephritis. J Infect 2011;62:159-64.
64. Jeon JH, Kim K, Han WD, Song SH, Park KU, Rhee JE, Song KH, Park WB, Kim ES, Park SW, Kim NJ, Oh MD, Kim HB. Empirical use of ciprofloxacin for acute uncomplicated pyelonephritis caused by *Escherichia coli* in communities where the prevalence of fluoroquinolone resistance is high. Antimicrob Agents Chemother 2012;56:3043-6.
65. Chen YH, Ko WC, Hsueh PR. The role of fluoroquinolones in the management of urinary tract infections in areas with high rates of fluoroquinolone-resistant uropathogens. Eur J Clin Microbiol Infect Dis 2012;31:1699-704.

66. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44 (Suppl 2):S27-72.
67. Song JH, Kang MW, Kim DJ, Pai H, Suh JY, Shim TS, Ahn JH, Ahn.C.M., Woo JH, Lee NY, Lee DG, Lee MS, Lee SM, Lee YS, Lee H, Chung DR, a Joint committee for CAP Treatment Guideline. Treatment guidelines for community-acquired pneumonia in Korea: an evidence-based approach to appropriate antimicrobial therapy. Infect Chemother 2009;41:133-53.
68. Low DE. Quinolone resistance among pneumococci: therapeutic and diagnostic implications. Clin Infect Dis 2004; 38 (Suppl 4):S357-62.
69. Jenkins SG, Brown SD, Farrell DJ. Trends in antibacterial resistance among *Streptococcus pneumoniae* isolated in the USA: update from PROTEKT US years 1-4. Ann Clin Microbiol Antimicrob 2008;7:1.
70. Patel SN, McGeer A, Melano R, Tyrrell GJ, Green K, Pillai DR, Low DE; Canadian Bacterial Surveillance Network. Susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. Antimicrob Agents Chemother 2011;55:3703-8.
71. European Centre for Disease Prevention and Control (ECDC). Antimicrobial resistance surveillance in Europe 2012. Available at: http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-surveillance-europe-2012.pdf. Accessed 2 December 2014.
72. Jacobs E, Dalhoff A, Korfmann G. Susceptibility patterns of bacterial isolates from hospitalised patients with respiratory tract infections (MOXIAKTIV Study). Int J Antimicrob Agents 2009;33:52-7.
73. Pletz MW, van der Linden M, von Baum H, Duesberg CB, Klugman KP, Welte T; CAPNETZ study group. Low prevalence of fluoroquinolone resistant strains and resistance precursor strains in *Streptococcus pneumoniae* from patients with community-acquired pneumonia despite high fluoroquinolone usage. Int J Med Microbiol 2011;301:53-7.
74. Kim SH, Song JH, Chung DR, Thamlikitkul V, Yang Y, Wang H, Lu M, So TM, Hsueh PR, Yasin RM, Carlos CC, Pham HV, Lalitha MK, Shimono N, Perera J, Shibl AM, Baek JY, Kang CI, Ko KS, Peck KR; ANSORP Study Group. Changing trends in antimicrobial resistance and serotypes of *Streptococcus pneumoniae* isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. Antimicrob Agents Chemother 2012;56:1418-26.
75. Jiménez MR, Bellido JL, García Rodríguez JA. Risk factors associated with colonization by pneumococci with reduced susceptibility to fluoroquinolones in adult outpatients. J Clin Microbiol 2005;43:1193-7.
76. Ho PL, Tse WS, Tsang KW, Kwok TK, Ng TK, Cheng VC, Chan RM. Risk factors for acquisition of levofloxacin-resistant *Streptococcus pneumoniae*: a case-control study. Clin Infect Dis 2001;32:701-7.
77. Kang CI, Song JH, Kim SH, Chung DR, Peck KR, So TM, Hsueh PR; ANSORP Study Group. Risk factors for levofloxacin-nonsusceptible *Streptococcus pneumoniae* in community-acquired pneumococcal pneumonia: a nested case-control study. Eur J Clin Microbiol Infect Dis 2014;33:55-9.
78. Kang CI, Song JH, Kim SH, Chung DR, Peck KR, Thamlikitkul V, Wang H, So TM, Hsueh PR, Yasin RM, Carlos CC, Van PH, Perera J; Asian Network for Surveillance of Resistant Pathogens (ANSORP) Study Group. Association of levofloxacin resistance with mortality in adult patients with invasive pneumococcal diseases: a post hoc analysis of a prospective cohort. Infection 2013;41:151-7.
79. de Cueto M, Rodríguez JM, Soriano MJ, López-Cerero L, Venero J, Pascual A. Fatal levofloxacin failure in treatment of a bacteremic patient infected with *Streptococcus pneumoniae* with a preexisting *parC* mutation. J Clin Microbiol 2008;46:1558-60.
80. Pfaller MA, Farrell DJ, Sader HS, Jones RN. AWARE Ceftaroline Surveillance Program (2008-2010): trends in resistance patterns among *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the United States. Clin Infect Dis 2012;55 (Suppl 3):S187-93.
81. Chung DR, Song JH, Kim SH, Thamlikitkul V, Huang SG, Wang H, So TM, Yasin RM, Hsueh PR, Carlos CC, Hsu LY, Buntaran L, Lalitha MK, Kim MJ, Choi JY, Kim SI, Ko KS, Kang CI, Peck KR; Asian Network for Surveillance of Resistant Pathogens Study Group. High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. Am J Respir Crit Care Med 2011;184:1409-17.
82. Karlowsky JA, Draghi DC, Jones ME, Thornsberry C, Friedland IR, Sahm DF. Surveillance for antimicrobial susceptibility among clinical isolates of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* from hospitalized patients in the United States, 1998 to 2001. Antimicrob Agents Chemother

2003;47:1681-8.
83. Jones ME, Draghi DC, Thornsberry C, Karlowsky JA, Sahm DF, Wenzel RP. Emerging resistance among bacterial pathogens in the intensive care unit-a European and North American surveillance study (2000-2002). Ann Clin Microbiol Antimicrob 2004;3:14.
84. Perez F, Hujer AM, Hujer KM, Decker BK, Rather PN, Bonomo RA. Global challenge of multidrug-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother 2007;51:3471-84.
85. Lagamayo EN. Antimicrobial resistance in major pathogens of hospital-acquired pneumonia in Asian countries. Am J Infect Control 2008;36 (4 Suppl):S101-8.
86. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, O'Neill PJ, Chow AW, Dellinger EP, Eachempati SR, Gorbach S, Hilfiker M, May AK, Nathens AB, Sawyer RG, Bartlett JG. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50:133-64.
87. Babinchak T, Badal R, Hoban D, Hackel M, Hawser S, Lob S, Bouchillon S. Trends in susceptibility of selected gram-negative bacilli isolated from intra-abdominal infections in North America: SMART 2005-2010. Diagn Microbiol Infect Dis 2013;76:379-81.
88. Hawser SP, Bouchillon SK, Hoban DJ, Badal RE, Cantón R, Baquero F. Incidence and antimicrobial susceptibility of *Escherichia coli* and *Klebsiella pneumoniae* with extended-spectrum beta-lactamases in community- and hospital-associated intra-abdominal infections in Europe: results of the 2008 Study for Monitoring Antimicrobial Resistance Trends (SMART). Antimicrob Agents Chemother 2010;54:3043-6.
89. Bochicchio GV, Baquero F, Hsueh PR, Paterson DL, Rossi F, Snyder TA, McCarroll K, Satishchandran V, Dinubile MJ, Chow JW. *In vitro* susceptibilities of *Escherichia coli* isolated from patients with intra-abdominal infections worldwide in 2002-2004: results from SMART (Study for Monitoring Antimicrobial Resistance Trends). Surg Infect (Larchmt) 2006;7:537-45.
90. Ko WC, Hsueh PR. Increasing extended-spectrum beta-lactamase production and quinolone resistance among Gram-negative bacilli causing intra-abdominal infections in the Asia/Pacific region: data from the smart study 2002-2006. J Infect 2009;59:95-103.
91. Yang Q, Wang H, Chen M, Ni Y, Yu Y, Hu B, Sun Z, Huang W, Hu Y, Ye H, Badal RE, Xu Y. Surveillance of antimicrobial susceptibility of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in China: the 2002-2009 Study for Monitoring Antimicrobial Resistance Trends (SMART). Int J Antimicrob Agents 2010;36:507-12.
92. Kang CI, Chung DR, Ko KS, Peck KR, Song JH; Korean Network for the Study of Infectious Diseases (KONSID). Risk factors for mortality and impact of broad-spectrum cephalosporin resistance on outcome in bacteraemic intra-abdominal infections caused by Gram-negative bacilli. Scand J Infect Dis 2011;43:202-8.
93. Yagci D, Yoruk F, Azap A, Memikoglu O. Prevalence and risk factors for selection of quinolone-resistant *Escherichia coli* strains in fecal flora of patients receiving quinolone therapy. Antimicrob Agents Chemother 2009;53:1287-9.
94. Garau J, Xercavins M, Rodríguez-Carballeira M, Gómez-Vera JR, Coll I, Vidal D, Llovet T, Ruíz-Bremón A. Emergence and dissemination of quinolone-resistant *Escherichia coli* in the community. Antimicrob Agents Chemother 1999;43:2736-41.
95. Nagy E, Urbán E, Nord CE; ESCMID Study Group on Antimicrobial Resistance in Anaerobic Bacteria. Antimicrobial susceptibility of *Bacteroides fragilis* group isolates in Europe: 20 years of experience. Clin Microbiol Infect 2011;17:371-9.
96. Low DE. Clinical Relevance of Quinolone Resistance. In: Hooper DC, Rubinstein E, eds. Quinolone Antimicrobial Agents. 3rd ed. Washington, DC: American Society for Microbiology Press; 2003;355-86.
97. Parry CM, Threlfall EJ. Antimicrobial resistance in typhoidal and nontyphoidal salmonellae. Curr Opin Infect Dis 2008;21:531-8.
98. Gu B, Cao Y, Pan S, Zhuang L, Yu R, Peng Z, Qian H, Wei Y, Zhao L, Liu G, Tong M. Comparison of the prevalence and changing resistance to nalidixic acid and ciprofloxacin of *Shigella* between Europe-America and Asia-Africa from 1998 to 2009. Int J Antimicrob Agents 2012;40:9-17.
99. Horiuchi S, Inagaki Y, Yamamoto N, Okamura N, Imagawa Y, Nakaya R. Reduced susceptibilities of *Shigella sonnei* strains isolated from patients with dysentery to fluoroquinolones. Antimicrob Agents Chemother 1993;37:2486-9.
100. Vinh H, Wain J, Chinh MT, Tam CT, Trang PT, Nga D, Echeverria P, Diep TS, White NJ, Parry CM. Treatment of bacillary dysentery in Vietnamese children: two doses of ofloxacin versus 5-days nalidixic acid. Trans R Soc Trop Med Hyg 2000;94:323-6.

101. Khan WA, Seas C, Dhar U, Salam MA, Bennish ML. Treatment of shigellosis: V. Comparison of azithromycin and ciprofloxacin. A double-blind, randomized, controlled trial. Ann Intern Med 1997;126:697-703.
102. Ge B, Wang F, Sjolund-Karlsson M, McDermott PF. Antimicrobial resistance in *Campylobacter*: susceptibility testing methods and resistance trends. J Microbiol Methods 2013;95:57-67.
103. Shin E, Oh Y, Kim M, Jung J, Lee Y. Antimicrobial resistance patterns and corresponding multilocus sequence types of the *Campylobacter jejuni* isolates from human diarrheal samples. Microb Drug Resist 2013;19:110-6.
104. Goodman LJ, Trenholme GM, Kaplan RL, Segreti J, Hines D, Petrak R, Nelson JA, Mayer KW, Landau W, Parkhurst GW, Levin S. Empiric antimicrobial therapy of domestically acquired acute diarrhea in urban adults. Arch Intern Med 1990;150:541-6.
105. Kuschner RA, Trofa AF, Thomas RJ, Hoge CW, Pitarangsi C, Amato S, Olafson RP, Echeverria P, Sadoff JC, Taylor DN. Use of azithromycin for the treatment of Campylobacter enteritis in travelers to Thailand, an area where ciprofloxacin resistance is prevalent. Clin Infect Dis 1995;21:536-41.
106. Karchmer AW. Treatment of skin and soft tissue infections. In: Hooper DC, Rubinstein E, eds. Quinolone Antimicrobial Agents. 3rd ed. Washington, DC: American Society for Microbiology Press; 2003;311-21.
107. Dalhoff A. Resistance surveillance studies: a multifaceted problem-the fluoroquinolone example. Infection 2012;40:239-62.
108. Montes M, Tamayo E, Orden B, Larruskain J, Perez-Trallero E. Prevalence and clonal characterization of *Streptococcus pyogenes* clinical isolates with reduced fluoroquinolone susceptibility in Spain. Antimicrob Agents Chemother 2010;54:93-7.
109. Van Heirstraeten L, Leten G, Lammens C, Goossens H, Malhotra-Kumar S. Increase in fluoroquinolone non-susceptibility among clinical *Streptococcus pyogenes* in Belgium during 2007-10. J Antimicrob Chemother 2012;67:2602-5.
110. Barry AL, Jones RN. *In vitro* activity of ciprofloxacin against gram-positive cocci. Am J Med 1987;82:27-32.
111. Smith SM. *In vitro* comparison of A-56619, A-56620, amifloxacin, ciprofloxacin, enoxacin, norfloxacin, and ofloxacin against methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 1986;29:325-6.
112. Flamm RK, Farrell DJ, Mendes RE, Ross JE, Sader HS, Jones RN. LEADER surveillance program results for 2010: an activity and spectrum analysis of linezolid using 6801 clinical isolates from the United States (61 medical centers). Diagn Microbiol Infect Dis 2012;74:54-61.
113. Kim ES, Lee HJ, Chung GT, Lee YS, Shin DH, Jung SI, Song KH, Park WB, Kim NJ, Park KU, Kim EC, Oh MD, Kim HB. Molecular characterization of methicillin-resistant *Staphylococcus aureus* isolates in Korea. J Clin Microbiol 2011;49:1979-82.
114. Jones RN, Mendes RE, Sader HS. Ceftaroline activity against pathogens associated with complicated skin and skin structure infections: results from an international surveillance study. J Antimicrob Chemother 2010;65 (Suppl 4):iv17-31.
115. Naimi TS, LeDell KH, Como-Sabetti K, Borchardt SM, Boxrud DJ, Etienne J, Johnson SK, Vandenesch F, Fridkin S, O'Boyle C, Danila RN, Lynfield R. Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. JAMA 2003;290:2976-84.
116. Moran GJ, Krishnadasan A, Gorwitz RJ, Fosheim GE, McDougal LK, Carey RB, Talan DA; EMERGEncy ID Net Study Group. Methicillin-resistant *S. aureus* infections among patients in the emergency department. N Engl J Med 2006;355:666-74.
117. Mendes RE, Sader HS, Deshpande LM, Diep BA, Chambers HF, Jones RN. Characterization of baseline methicillin-resistant *Staphylococcus aureus* isolates recovered from phase IV clinical trial for linezolid. J Clin Microbiol 2010;48:568-74.
118. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, Deery HG, Embil JM, Joseph WS, Karchmer AW, Pinzur MS, Senneville E, Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54:e132-73.
119. Kim BN, Kim ES, Oh MD. Oral antibiotic treatment of staphylococcal bone and joint infections in adults. J Antimicrob Chemother 2014;69:309-22.
120. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 2014;59:147-59.
121. Centers for Disease Control and Prevention (CDC). Antibiotic-resistant gonorrhea basic information. Available at: http://www.cdc.gov/std/gonorrhea/arg/basic.htm. Ac-

cessed 2 December 2014.
122. Lee H, Hong SG, Soe Y, Yong D, Jeong SH, Lee K, Chong Y. Trends in antimicrobial resistance of *Neisseria gonorrhoeae* isolated from Korean patients from 2000 to 2006. Sex Transm Dis 2011;38:1082-6.
123. Rahman M, Alam A, Nessa K, Nahar S, Dutta DK, Yasmin L, Monira S, Sultan Z, Khan SA, Albert MJ. Treatment failure with the use of ciprofloxacin for gonorrhea correlates with the prevalence of fluoroquinolone-resistant Neisseria gonorrhoeae strains in Bangladesh. Clin Infect Dis 2001;32:884-9.
124. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59:1-110.