GyrA mutations in Fluoroquinolone Resistant Clostridium difficile
PCR 027

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gyrA Mutations in Fluoroquinolone-resistant Clostridium difficile PCR-027

To the Editor: Clostridium difficile is the most common cause of bacterial diarrhea in hospitalized patients (1). Antimicrobial drug therapy is the most important risk factor associated with the acquisition of C. difficile, and several antimicrobial agents including clindamycin, amoxicillin, and cephalosporins have been particularly associated with C. difficile infection (2). Acquisition of resistance to clindamycin is considered 1 mechanism whereby clonal strains emerge and predominate in healthcare environments (3). Historically, fluoroquinolone antimicrobial agents were considered low risk for C. difficile-associated-disease; however, recent studies indicate a shift in the risk associated with their use (4). Furthermore, recent outbreaks in Canada and the United States have been associated with fluoroquinolone exposure (4).

Recently, several C. difficile outbreaks due to PCR ribotype 027 (PCR-027) and associated with increased disease severity and death have been reported worldwide (4). This strain type contains the genes for binary toxin and has an 18-bp deletion and a frameshift mutation in tcdC hypothesized to result in deregulated expression of toxins A and B. These strains produce 16× more toxin A and 23× more toxin B in vitro than toxino-type 0 strains (5). These isolates demonstrate universal high-level resistance to fluoroquinolones in contrast to that of PCR 027 isolates collected before 2001 (4).

We report the mechanism of fluoroquinolone resistance in a cluster (n = 5) of Irish PCR-027 C. difficile isolates that were characterized by using toxino-typing and 16–23S ribotyping. Amplification with PCR and sequencing was used to identify the binary toxin gene (cdtB) and an 18-bp deletion and a frameshift mutation at position 117 in the tcdC gene. Antimicrobial susceptibility to 5 fluoroquinolone antimicrobial drugs was determined with E-tests (AB-Biodisk, Solna, Sweden). The quinolone-resistance–determining region (QRDR) of DNA gyrase and topoisomerase IV have been associated with increased resistance to fluoroquinolones in several bacteria (6). This report identifies for the first time a mutation in gyrA that is associated with high-level resistance to fluoroquinolones in C. difficile PCR-027. In Escherichia coli, amino acid substitutions that occur at Ser-83 in gyrA have been associated with fluoroquinolone resistance (6). Thr-82 in C. difficile corresponds to Ser-83 in E. coli. Thr-82-Val amino acid substitutions corresponding to Ser-83 have been associated with fluoroquinolone resistance in several bacteria, including Pseudomonas aeruginosa, Enterobacter aerogenes, Campylobacter jejuni, and C. difficile (6). Ackermann et al. described 2 mutations in gyrA that resulted in an amino acid substitution corresponding to codon 83 in E. coli. Thirteen of the 18 C. difficile isolates had the Thr-82-Val substitution, and 1 strain had a Thr-82-Val substitution (7). Dridi et al. described this Thr-82-Val GyrA substitution in 6 resistant C. difficile strains corresponding to 3 serogroups, H1, A9, and 1C (8).

Early studies investigating fluoroquinolone antimicrobial agents suggested that most C. difficile isolates were susceptible to these drugs.

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Antimicrobial drug resistance to this class has increased with fluoroquinolone use, and currently these drugs remain the most frequently prescribed antimicrobial agents in the United States and Europe. Acquired resistance to the newer fluoroquinolone antimicrobial agents is not restricted to ribotype PCR-027, although different amino acid substitutions in the QRDR of gyrA and gyrB have been described (7–9). Wilcox et al. have described high-level fluoroquinolone resistance in PCR ribotype-001, an endemic strain type found in several healthcare settings in the United Kingdom (10). We have previously described the emergence of a fluoroquinolone-resistant toxin A–, toxin B–positive strain in Dublin (9).

We report a mutation in gyrA associated with fluoroquinolone resistance in C. difficile PCR-027. Antimicrobial drug resistance in C. difficile isolates must be monitored because the emergence of universal fluoroquinolone resistance in different C. difficile strain types may be a factor promoting outbreaks in hospitals. As exposure to several different fluoroquinolone antimicrobial drugs have been independently associated with C. difficile–associated-disease, restricted use of all fluoroquinolones, rather than changing from 1 quinolone to another, may be a necessary step toward preventing and controlling C. difficile outbreaks.

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